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Mesoporous Silica Nanoparticles: A Review of Synthetic Design and Immunomodulatory Applications

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Abstract

Mesoporous silica nanoparticles (MSNs) are tiny, sponge-like particles made from silica that are attracting attention for their ability to influence the immune system. Thanks to their adjustable shape, size, and surface features, MSNs can be designed to carry medicines, vaccine ingredients, or immune-boosting agents to specific parts of the body at the right time. This review explains how MSNs are being explored in three major areas: cancer treatment, controlling inflammation, and improving vaccine performance. It describes how these particles interact with immune cells and how they can help activate or calm immune responses in a targeted way. Examples include using MSNs to reach key immune cells, reduce harmful inflammation, and strengthen how vaccines work. The article also discusses current challenges—such as how long MSNs stay in the body and whether they cause unwanted immune reactions—and presents new ideas to solve these issues. Overall, MSNs show promise as flexible tools for developing safer and more effective immune therapies.

Keywords: Mesoporous silica nanoparticles, Immunomodulation, Cancer immunotherapy, Vaccine delivery, Inflammatory diseases.

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Introduction

Mesoporous silica nanoparticles (MSNs) are silicon dioxide–based nanostructures with highly ordered pores ranging from 2 to 50 nm. Their large surface area, adjustable pore size, and excellent biocompatibility make them ideal for drug delivery, catalysis, and biomedical imaging. MSNs are typically synthesized using template-assisted methods involving surfactants like CTAB and precursors such as TEOS, with synthesis conditions shaping their size, morphology, and porosity. Well-known MSN types include MCM-41, MCM-48, SBA-15, SBA-16, FSM-16, and TUD-1—each offering unique structural features tailored to specific therapeutic and diagnostic needs [1,2]. MSNs are primarily synthesized via sol–gel methods, where silicon alkoxides such as TEOS undergo hydrolysis and condensation in the presence of surfactants like cetyltrimethylammonium bromide (CTAB), which act as structure-directing agents to form ordered mesoporous frameworks such as MCM-41 and SBA-15 (Figure 1) [3]. Additional synthesis strategies include soft and hard templating, modified Stöber methods, and hydrothermal approaches, each enabling control over particle size, morphology, and pore architecture for specific applications in drug delivery, catalysis, and imaging. Key parameters, including pH, temperature, surfactant concentration, and aging time, critically influence the mesostructure and dispersity of MSNs, with alkaline conditions favoring rapid condensation and micelle formation. The kinetic mechanism involves TEOS hydrolysis, micelle formation, and silica condensation around surfactant assemblies, with stirring and ionic strength affecting reproducibility and uniformity [3,4]. MSNs are highly versatile nanomaterials with tunable pore structures, large surface areas, and modifiable surfaces, enabling applications across catalysis, environmental remediation, agriculture, energy, and biomedicine. In catalysis, they support metal nanoparticles and enzymes, enhancing reaction efficiency [5]. Their high adsorption capacity makes them effective in removing pollutants from water, while in agriculture, they enable controlled release of fertilizers and pesticides, improving sustainability. MSNs also contribute to energy storage by facilitating ion transport in batteries and supercapacitors. Among the most advanced applications of MSNs are in biomedicine and immunotherapy. In biomedicine, MSNs serve as advanced drug delivery platforms for cancer therapy, gene transfer, and antimicrobial treatments [6–8]. Their surface can be engineered to evade immune detection or actively engage immune cells, making them ideal carriers for antigens, adjuvants, and immunomodulators [9]. With low immunogenicity and favorable biodegradability, MSNs support safe clinical integration and offer a promising foundation for precision immunomodulation in oncology, autoimmunity, and infectious disease. This review is structured to guide readers through the multifaceted role of mesoporous silica nanoparticles (MSNs) in immunotherapy. We begin by examining how specific physicochemical features—such as pore size, surface chemistry, and functionalization—govern MSN interactions with both innate and adaptive immune cells. Next, we explore their therapeutic

applications, including cancer immunotherapy, autoimmune regulation, and vaccine delivery, highlighting how MSNs are engineered to modulate immune responses with precision. Finally, we discuss current design challenges such as biodegradability, targeting specificity, and safety, and conclude with future directions for developing personalized MSN-based immunotherapies tailored to individual immune profiles.

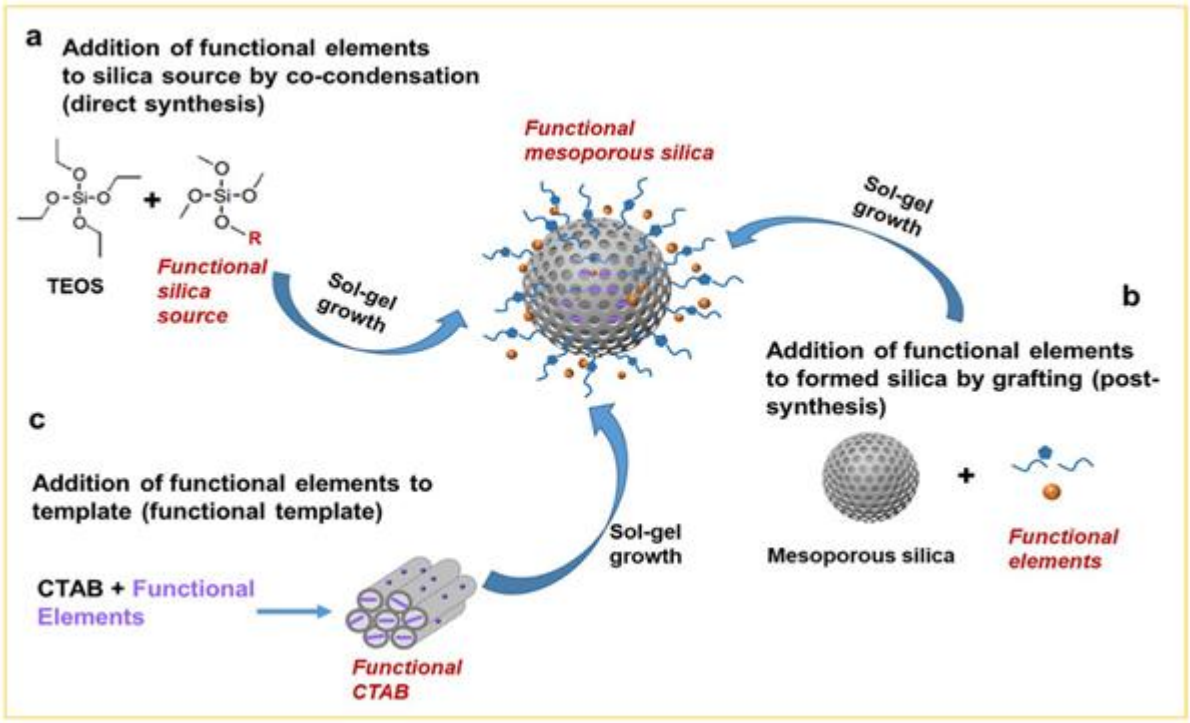

Figure 1. MCM-41 functionalization via sol–gel can occur at three stages: (a) co-condensation during synthesis, (b) post-synthesis grafting, and (c) functional template incorporation. [3].

Physicochemical Properties of MSNs Relevant to Immunology

MSNs represent a versatile class of inorganic nanomaterials characterized by a highly organized porous architecture, typically featuring pore diameters between 2 and 50 nanometers. This structural configuration offers an expansive surface area—often exceeding 700 m^2/g—and enables precise control over pore size, which is critical for accommodating diverse therapeutic agents, such as small peptides, molecules, and nucleic acids [10-15]. Particle size and morphology play a crucial role in determining the biological fate of MSNs. Studies have shown that particles with a uniform size of 50-200 nm are most effective in being taken up by dendritic cells and macrophages, while also minimizing off-target clearance [16]. Beyond size, anisotropic shapes—such as rod- and worm-like architectures—prolong systemic circulation and enhance lymph node trafficking by reducing recognition and sequestration by the mononuclear phagocyte system [17]. MSNs possess exceptionally extensive internal surface areas and pore volumes reaching up to 1.5 cm^3/g, which translates into remarkable drug loading capacities for small-molecule therapeutics. Recent studies

have demonstrated that such structural attributes enable drug payloads to constitute 30–40 wt% of the total particle mass without compromising colloidal stability or particle Integrity (Figure 2) [18].

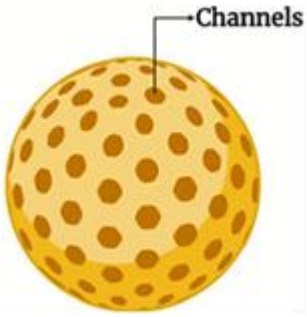

Figure 2. Mesoporous channels promote efficient drug diffusion and controlled release [18].

Precise control of pore diameter via surfactant-templated synthesis allows matching of the mesopore size (2–20 nm) to the hydrodynamic dimensions of peptide and protein antigens. This tailoring has yielded antigen encapsulation efficiencies exceeding 75%, facilitating dense antigen presentation within endosomal compartments and enhancing subsequent T-cell priming in preclinical models [17]. Beyond geometric tuning, functionalization strategies such as co-condensation of organosilanes and post-synthesis grafting introduce amine, thiol, or hydrophobic groups along the pore walls. These moieties strengthen electrostatic and hydrogen-bonding interactions, boosting peptide loading by nearly 50% and further increasing small-molecule drug entrapment and stability within the mesopores [19]. Due to the inclusion of pH-sensitive linkers, such as benzoic-imine or orthoester, MSNs are able to maintain structural stability in physiological pH conditions, while also undergoing disassembly in acidic environments (≤ 6.5). This allows for controlled drug release in specific cellular compartments. [18]. Concurrently, disulfide cross-linkers exploit the high intracellular glutathione (GSH) concentration (~ 10 mM) to cleave S–S bonds, disassembling the nanoparticle framework and releasing over 75 % of encapsulated therapeutics within two hours, while remaining inert under low extracellular GSH levels (~ 2 μM) to minimize off-target leakage [20,21]. Enzyme-responsive MSNs utilize peptide or polysaccharide caps that are selectively cleaved by disease-associated enzymes for spatially precise release. For instance, MSNs cloaked with matrix metalloproteinase (MMP)-sensitive peptide sequences remain occluded in healthy tissues but open in MMP-rich pathological sites to deliver growth factors for bone regeneration [16]. Similarly, pectin-coated dendritic MSNs loaded with eugenol exhibit pH, temperature, and pectinase dual responsiveness; in the presence of pectinase, the polysaccharide shell is degraded, enabling sustained biocide delivery and enhanced antibacterial efficacy against tomato bacterial wilt [22]. Beyond endogenous cues, exogenous stimuli such as light afford remote, on-demand control over MSN cargo release. MSNs functionalized with azobenzene gatekeepers

undergo reversible cis–trans isomerization under UV/visible irradiation, opening pore channels to release payloads within minutes while remaining sealed in the dark [16]. Combining photo-responsive moieties with pH- and enzyme-sensitive coatings yields multifunctional platforms capable of sequential or synergistic release, thus maximizing therapeutic index and minimizing systemic toxicity [18,21].

Cancer Immunotherapy Platforms Using MSNs

Cancer immunotherapy enhances the body's ability to recognize and eliminate cancer cells through strategies such as immune checkpoint blockade, CAR T-cell therapy, therapeutic vaccination, and oncolytic virotherapy. These approaches rely on coordinated activation of both innate and adaptive immune responses. MSN-based platforms contribute by modulating key immune cells—including dendritic cells (antigen-presenting cells that initiate T-cell responses), macrophages (phagocytic cells involved in inflammation and tumor clearance), $CD4^+$ and $CD8^+$ T cells (helper and cytotoxic lymphocytes), regulatory T cells (immune suppressors), B cells (antibody producers), natural killer (NK) cells (innate cytotoxic cells), myeloid-derived suppressor cells (MDSCs; immunosuppressive regulators), microglia (CNS-resident macrophages), and neutrophils (first-line responders and modulators of inflammation). These cells interact through signaling pathways such as NF-κB (inflammatory gene regulation), STING–TBK1–IRF3 (type I interferon induction), NLRP3 inflammasome (IL-1β/IL-18 production), CD47–SIRPα (phagocytosis inhibition), TLR4 (pathogen recognition), and JAK/STAT (cytokine signaling), as well as immunogenic cell death signals like calreticulin exposure and HMGB1/ATP release. Together, these components form the mechanistic basis for MSN-mediated control of immune responses in cancer therapy, inflammatory disease modulation, and vaccine development. The following subsections categorize key strategies based on therapeutic mechanisms and nanoparticle design:

Photothermal and Photodynamic Immunotherapy

Wang, Wang, Huang, and An designed MSNs loaded with gold nanodots to create a self-amplifying depot for photothermal immunotherapy. Upon near-infrared irradiation, the gold nanodots generated localized heat, triggering immunogenic cell death (ICD) and enhancing antigen presentation. This thermal effect also promoted the release of immunostimulatory agents from the MSNs, amplifying the immune response against tumors. The platform demonstrated significant tumor suppression and immune activation in preclinical models, offering a promising strategy for synergistic photothermal and immunotherapeutic cancer treatment (Figure 3) [23].

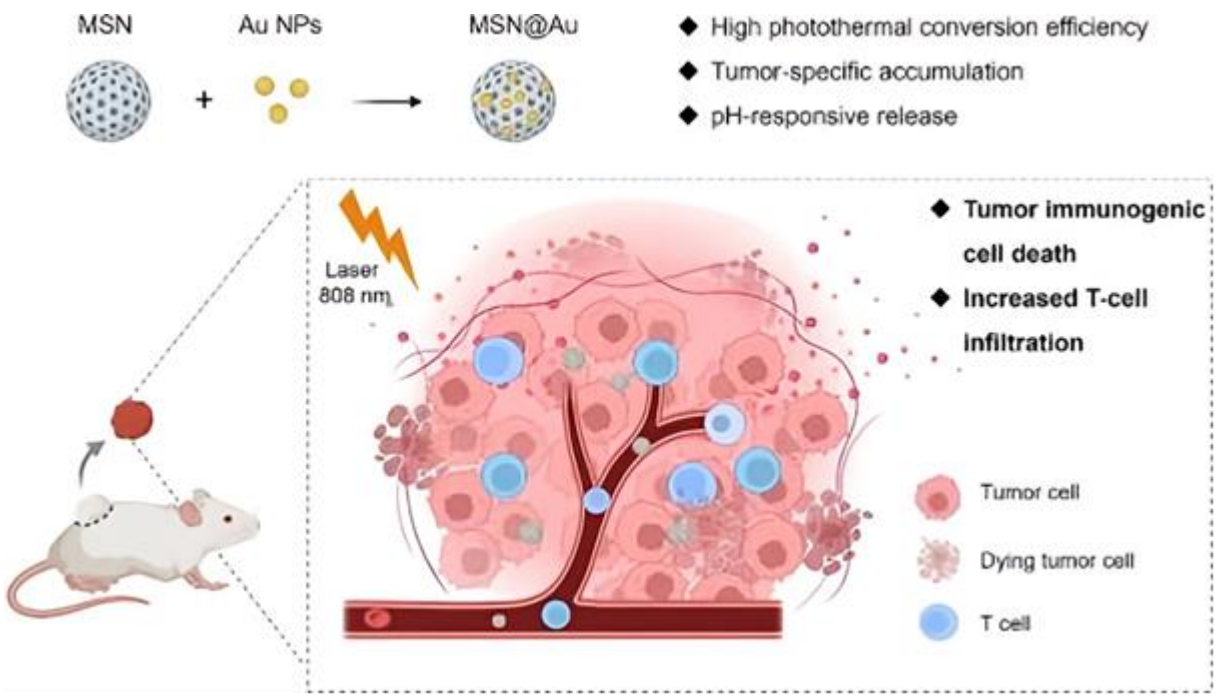

Figure 3. Schematic illustration of MSN@Au-mediated photothermal immunotherapy [23].

Several multifunctional MSN-based platforms have been developed to integrate phototherapy with cancer immunotherapy. ALUMSNs combine upconversion cores and Bi_2Se_3 for synergistic photodynamic and photothermal therapy, supported by tumor-targeting coatings and multimodal imaging capabilities [24]. Li et al. designed hollow HMSNs that co-deliver photosensitizers and immune adjuvants, enhancing ROS generation and dendritic cell activation for effective tumor suppression [25]. A nanovaccine system with OVA-loaded MSNs, ammonium bicarbonate, and polydopamine enables photothermal-induced antigen release and systemic immune activation, achieving 75% complete remission in melanoma models [26]. Ding et al. introduced UCNP-coated MSNs for co-delivery of chlorin e6 and tumor antigens, triggering immunogenic cell death and robust T-cell responses under NIR light [27]. These platforms demonstrate the potential of MSN-based systems to synergize phototherapy and immunomodulation for enhanced cancer treatment.

Immune Checkpoint Inhibition and Genetic Editing

Two advanced MSN-based platforms have demonstrated synergistic strategies for targeted cancer immunotherapy. One system combines tumor cell membrane-coated mesoporous silicon nanoparticles with CRISPR/Cas9-mediated PD-L1 knockout, enabling precise tumor targeting and enhanced T-cell activation through immune checkpoint suppression [28]. Another approach, aCD47-DMSN, co-delivers doxorubicin and anti-CD47 antibodies to simultaneously disrupt the CD47–SIRPα axis and induce immunogenic cell death. This dual targeting promotes macrophage-mediated phagocytosis, antigen presentation, and robust $CD8^+$ T cell activation. Both platforms

showed strong therapeutic efficacy in preclinical models, highlighting their potential for precision chemo-immunotherapy [29].

Antigen and Adjuvant Co-Delivery

Multiple MSN-based platforms have been developed to co-deliver antigens and adjuvants for enhanced cancer immunotherapy. Lipid-coated MSNs improve lymph node targeting and antigen uptake by APCs, boosting dendritic cell activation and T-cell responses [30]. Amine-functionalized MSNs enable simultaneous loading of tumor antigens and CpG adjuvants, promoting potent $CD8^+$ T-cell immunity against hepatocellular carcinoma with minimal toxicity [31]. Dendritic MSNs (DMSNs) with branched pore structures enhance immunomodulator loading and release, improving antigen presentation and T-cell activation [32]. Additionally, bMSNs and c-di-GMP-loaded MSNs activate the STING–TBK1–IRF3 pathway, amplifying innate immune signaling and inducing robust antitumor responses. These platforms highlight the versatility of MSN architecture in designing next-generation nanovaccines (Figure 4) [33].

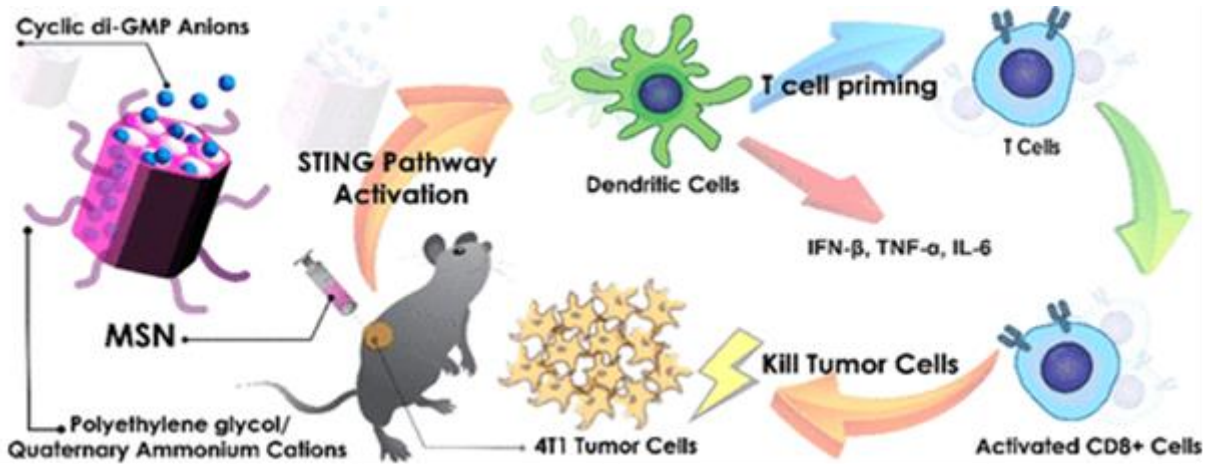

Figure 4. Schematic of c-di-GMP-loaded MSN enhancing STING-mediated immunotherapy in breast cancer [33].

Tumor Microenvironment Modulation

To enhance antitumor immunity, Xu et al. designed PEG-MSN-Stattic nanoparticles that deliver a STAT3 inhibitor directly to tumors, effectively depleting MDSCs and boosting cytotoxic T-cell infiltration, which improved immune checkpoint blockade outcomes [34]. In another study, MSNs were shown to activate the TLR4–NFκB pathway, triggering localized inflammation and reversing immune suppression, thereby sensitizing tumors to anti-PD-1 therapy [35]. Additionally, Duan and colleagues developed a hybrid MSN-MOF system that remains stable under normal conditions but releases immunostimulatory agents in acidic tumor environments. This responsive platform

promoted dendritic cell maturation and strong T-cell activation, offering a precise and effective strategy for cancer immunotherapy [36].

Vaccine Platforms and mRNA Delivery

Two innovative MSN-based platforms have advanced cancer vaccine delivery and immune activation. In one approach, MSNs loaded with the PKR inhibitor C16 enhance mRNA translation by suppressing innate immune barriers, leading to superior protein expression and potent antitumor responses in mouse models using ovalbumin and GM-CSF mRNA [37]. In another strategy, biodegradable bMSNs co-encapsulate neoantigens, CpG adjuvants, and chlorin e6 for PET-guided photodynamic therapy and personalized immunotherapy. Laser-triggered release activates dendritic cells and neoantigen-specific T-cell responses, effectively targeting both primary and metastatic tumors [38].

Hybrid and Biodegradable Systems

Several hybrid and biodegradable MSN platforms have been developed to combine cancer therapy with immune activation. Thin-shell hollow MSNs enable pH-triggered doxorubicin release and, when paired with anti-CTLA4 therapy, promote tumor suppression and systemic immune responses [39]. Carbon-dot embedded MSNs degrade under NIR light, releasing immunogenic debris that boosts dendritic cell activation [40]. Gold-doped MSNs deliver CpG directly to tumors and use photothermal heating to generate antigens in situ, amplifying immune responses [41]. Meanwhile, AB@MSNs release hydrogen gas in acidic tumor environments, showing strong anticancer effects through oxidative stress modulation [42].

Treatment of Inflammatory Diseases Using MSNs

Inflammatory diseases—such as rheumatoid arthritis, IBD, and neuroinflammation—are marked by chronic immune activation and tissue damage, often fueled by dysregulated pathways like NF-κB and inflammasome signaling [43]. Mesoporous silica nanoparticles (MSNs), with their customizable structure and surface properties, offer a promising solution for targeted therapy. By delivering anti-inflammatory drugs, antioxidants, or siRNA directly to affected tissues, MSNs can enhance treatment precision while minimizing systemic side effects [44,45]. Recent advances in this field are organized around specific therapeutic targets and delivery strategies.

Gastrointestinal Inflammation and IBD

Recent advances in MSN-based therapies offer promising solutions for treating inflammatory bowel disease (IBD). One approach uses pH-responsive, CD44-targeting MSNs that release drugs

specifically in inflamed intestinal tissue, reducing cytokine levels and promoting mucosal healing [46]. Shi et al. introduced a drug-free biodegradable system (MON-PEI) that scavenges cell-free DNA and ROS, effectively reducing inflammation in colitis models without systemic toxicity [47]. Teruel and colleagues developed magnetic MSNs with azo gates for colon-targeted delivery of hydrocortisone, showing strong therapeutic effects when activated by the colon's reducing environment and guided magnetically [48]. Additionally, emulgel matrices reinforced with mesoporous silica improved flurbiprofen delivery by enhancing encapsulation and sustaining release, demonstrating the value of combining natural polymers with MSNs for gastroretentive drug systems [49].

Joint and Cartilage Inflammation

For rheumatoid arthritis, radially structured MSNs (RMSNs) functionalized with protonated amines have shown excellent potential as dexamethasone carriers. Their unique pore architecture allows high drug loading and sustained release—over 92% maintained for 100 hours—leading to significant inflammation reduction and cartilage repair in animal models [50]. In osteoarthritis treatment, bMSNs modified with PMPC offer both lubrication and anti-inflammatory effects. These particles degrade within a week, cut joint friction by half, and provide controlled drug release, making them strong candidates for intra-articular therapy [51].

Neuroinflammation and Brain Disorders

Co-delivery of epigallocatechin-3-gallate (EGCG) and MCC950 via MSNs significantly reduced inflammation and improved motor function in a Parkinson's disease model [52]. For spinal cord injury, ammonia borane-loaded MSNs enabled pH-triggered hydrogen release, promoting neuroprotection and microglial polarization toward an anti-inflammatory phenotype [53]. In intracerebral hemorrhage, lipid-coated magnetic MSNs doped with CeNPs offered both imaging and therapeutic benefits, reducing edema and improving neurological outcomes [54]. Ferrite–ceria nanoparticles with pH-responsive behavior further enhanced targeted anti-inflammatory effects, especially when integrated with MSNs [54]. Importantly, MSNs have demonstrated the ability to cross the blood–brain barrier under pathological conditions, making them valuable carriers for brain-targeted therapies in diseases like epilepsy and Alzheimer's [56].

Cardiovascular and Vascular Inflammation

MSN-based systems are paving the way for targeted treatment of vascular inflammation. One nanoplatform was designed for abdominal aortic aneurysm (AAA), delivering anti-inflammatory agents directly to inflamed vascular sites. This approach effectively reduced cytokine levels, limited

macrophage infiltration, and helped stabilize aneurysm progression in preclinical models [57]. In a separate study, engineered neutrophil apoptotic bodies (eNABs) were fused with MSNs carrying hexyl 5-aminolevulinate hydrochloride (HAL). This biomimetic system enabled targeted HAL delivery, promoting bilirubin synthesis in macrophages and enhancing inflammation resolution. The result was improved cardiac repair following myocardial infarction, demonstrating the regenerative and immunomodulatory potential of MSN-based platforms [58].

Skin and Transdermal Inflammation

A transdermal gel system incorporating etoricoxib-loaded MSNs has been developed to enhance the non-invasive delivery of anti-inflammatory agents. By optimizing the gel's physicochemical properties and evaluating its performance through ex vivo skin permeation, histopathological analysis, and in vivo anti-inflammatory studies, the formulation demonstrated significantly improved drug penetration and therapeutic efficacy. The MSN-based gel reduced inflammation in animal models while preserving skin integrity, highlighting its potential for sustained, targeted, and patient-friendly transdermal treatment of inflammatory conditions [59].

Bone Regeneration and Osteoimmune Modulation

Pollen-like MSNs (PMSNs) modulate macrophage immune responses to promote bone regeneration. Compared to smooth MSNs, PMSNs suppress pro-inflammatory gene and protein expression in RAW 264.7 cells, enhance CD28 signaling, and inhibit ERK phosphorylation. Despite similar uptake, PMSNs induce stronger anti-inflammatory effects and stimulate osteogenic differentiation in mBMSCs via BMP2 upregulation and mineralization. In vivo, PMSNs mitigate LPS-induced osteolysis, highlighting the role of nanoparticle surface topography in immunomodulation and bone repair (Figure 5) [60].

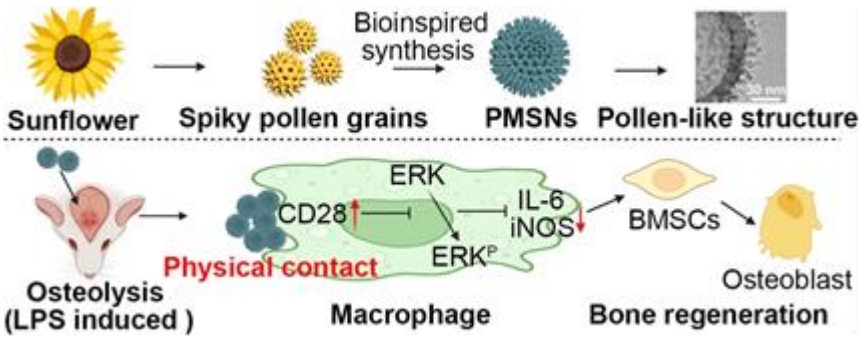

Figure 5. Pollen-like MSNs modulate macrophage anti-inflammatory activity via contact cues in osteoimmune niches [60].

Respiratory Inflammation

To address acute lung injury (ALI), researchers have developed gated mesoporous silica nanoparticles (MSNs) loaded with dexamethasone (Dex). These smart carriers respond to inflammatory signals in lung tissue, allowing precise and controlled drug release. In preclinical models, the system significantly reduced lung inflammation and tissue damage, outperforming conventional Dex delivery. This targeted approach highlights the potential of MSN-based therapies for localized and responsive treatment of respiratory disorders [61].

Systemic Inflammation and Sepsis

MSNs have shown great promise in inflammation-related disorders due to their ability to respond to pathological stimuli like ROS and pH, enabling controlled drug release at inflamed sites. Building on this, Xiong, Jia, and Liang developed polysaccharide-coated MSNs to treat sepsis. The coating not only improved biocompatibility but also provided immunomodulatory effects, helping the nanoparticles interact with immune cells and suppress pro-inflammatory cytokines. In sepsis models, this approach led to reduced systemic inflammation and improved survival outcomes, highlighting the potential of functionalized MSNs for targeted anti-inflammatory therapy [62].

General Anti-Inflammatory and Antioxidant Delivery

MSNs have been engineered to co-deliver curcumin and resveratrol for synergistic anti-inflammatory therapy in autoimmune diseases. This dual-loaded system showed superior suppression of IL-6 and TNF-α compared to single-agent treatments, along with enhanced cellular uptake and biocompatibility in both in vitro and in vivo models [63]. Separately, caffeine-loaded MSNs (CSNPs) demonstrated strong anti-inflammatory effects in LPS-activated macrophages, significantly reducing COX-2 and TNF-α levels. Beyond inflammation control, CSNPs also promoted wound healing in vitro, thanks to sustained caffeine release and targeted delivery. These findings reinforce the potential of MSNs as versatile carriers for natural anti-inflammatory compounds in nanomedicine [64].

Vaccines and Adjuvants Using MSNs

Vaccines are biological preparations designed to stimulate the immune system by introducing weakened, inactivated, or molecular components of pathogens—such as proteins, toxins, or nucleic acids—to confer protective immunity against infectious diseases [65]. Adjuvants are immunomodulatory agents incorporated into vaccine formulations to enhance the magnitude and duration of the immune response by activating APCs and modulating both humoral and cellular immunity [66-68]. MSNs have emerged as multifunctional platforms in vaccinology, serving both

as antigen carriers and adjuvants attributable to their tunable, pore structure, high surface area, and biocompatibility, which enable efficient antigen loading, sustained release, and targeted delivery to immune cells [69]. The following subsections organize recent advances based on vaccine type, delivery route, and nanoparticle design.

Viral Vaccines

MSNs enhance vaccine efficacy by promoting dendritic cell uptake and activating innate immune pathways, leading to stronger and longer-lasting immune responses. Their dual role as antigen carriers and adjuvants allows for reduced antigen doses and fewer boosters, addressing key limitations in conventional vaccine design. Recent studies highlight their versatility across various vaccine platforms. For monkeypox, silica nanoparticles carrying three recombinant antigens triggered robust antibody and T-cell responses in preclinical models [70]. Sun et al. developed dendritic MSNs (DMSNs) to co-deliver SARS-CoV-2 RBD and T-cell epitopes, achieving strong humoral and cellular immunity with excellent biocompatibility [71]. Another peptide-based COVID-19 vaccine using biodegradable MSNs showed enhanced antigen presentation and immune activation in mice [72]. For MERS-CoV, silane-functionalized MSNs were used to encapsulate plasmid DNA and mRNA vaccines. While codon-optimized pDNA alone induced the strongest antibody response, MSN encapsulation notably improved mRNA immunogenicity, underscoring their potential in nucleic acid vaccine delivery [73].

Veterinary and Aquaculture Vaccines

MSNs are gaining traction as versatile platforms for veterinary and parasitic vaccines. In aquaculture, nanoemulsions outperformed silica nanoparticles (SiNPs) in tilapia vaccines against Streptococcus agalactiae, due to better mucosal adhesion and immune stimulation, though SiNPs offered structural stability [74]. Hollow MSNs (HMSNs) enabled high antigen loading and sustained release in vaccines targeting pseudorabies [75] and foot-and-mouth disease virus-like particles (FMDV-VLPs), significantly boosting immune responses without toxicity [76]. For poultry, MSN-based oral vaccines targeting Clostridium perfringens showed enhanced protection and antibody production, especially with covalent antigen conjugation [77]. In tuberculosis models, MSNs mimicking extracellular vesicles successfully delivered key antigens and elicited strong immune responses (Figure 6) [78]. MSNs also improved recombinant subunit vaccines against Mycoplasma hyopneumoniae in pigs, outperforming conventional adjuvants with no adverse effects [79]. Finally, in parasitic infections like schistosomiasis, MSNs enhanced antigen presentation and immune activation, offering a potent and biocompatible alternative to traditional adjuvants [80].

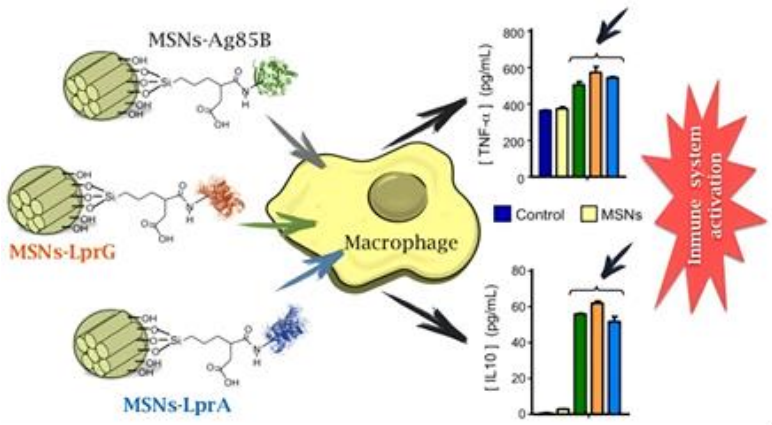

Figure 6. MSNs as a nanoplatform for tuberculosis vaccine delivery and immune activation [78].

Cancer Vaccines

MSNs, especially hollow and extra-large pore variants, have shown strong potential in cancer vaccine development by enhancing antigen loading, delivery, and immune activation. HMSNs with ultra-large mesopores effectively encapsulated biomolecules like ovalbumin and CpG, boosting dendritic cell uptake and antitumor immunity [81]. XL-MSNs (~25 nm pores) co-delivered protein antigens and TLR9 agonists directly to lymph nodes, triggering potent cytotoxic T-cell responses and tumor suppression [82]. Hybrid HMSNs coated with polyethylenimine (PEI) enabled efficient DNA vaccine delivery and self-adjuvanting effects, enhancing antigen expression and immune activation without external adjuvants [83]. Rambutan-like MSNs with spiky surfaces improved plasmid DNA transfection and elicited strong humoral and cellular responses (Figure 7) [84]. A systematic study confirmed that larger MSN pores significantly improve antigen delivery and immune stimulation, underscoring pore architecture as a key design factor for vaccine efficacy [85].

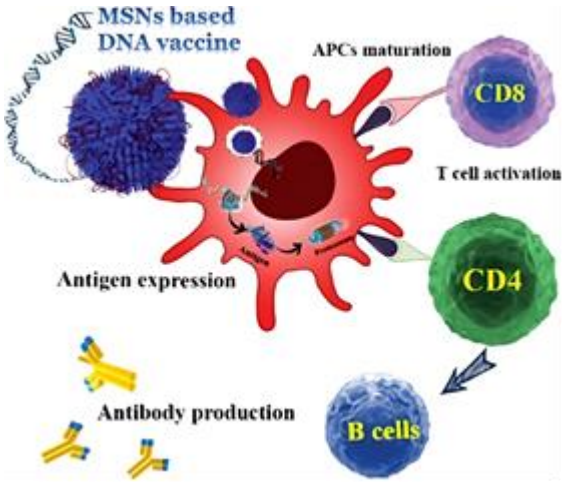

Figure 7. Rambutan-like MSNs facilitate DNA vaccine delivery and immune activation [84].

Oral and Mucosal Vaccines

MSNs offer a tunable platform for oral vaccine delivery by modulating particle size, surface properties, and release behavior. Smaller MSNs enhance antigen uptake and dendritic cell activation, while larger ones improve retention and systemic immunity in oral influenza vaccines [86]. In aquaculture, pH-responsive MSNs selectively release antigens in the acidic fish gut, boosting mucosal and systemic responses and enabling non-invasive vaccination [87]. Compared to carbon-based carriers, MSNs significantly improved antigen stability and immune protection in an oral cholera vaccine model, elevating IgG and IgA levels and reducing intestinal fluid loss [88].

Adjuvant Optimization and Morphology Studies

Mesoporous silica structures, such as SBA-15 and SBA-16, have shown potential as adjuvants for improving vaccine effectiveness. In diphtheria toxoid vaccines, rod-shaped SBA-15 particles are more effective than spherical ones in promoting antigen uptake and immune activation, emphasizing the significance of particle morphology [89]. In addition, SBA-16 nanoparticles have been successfully used in vaccines against Paracoccidioides brasiliensis, demonstrating a significant enhancement in cellular immunity and cytokine production, while also maintaining biocompatibility and stability. This supports the potential use of SBA-16 in fungal vaccine formulations [90].

Allergy and Immune Modulation

Hollow mesoporous silica nanoparticles (HMSNs) have shown promise in allergen-specific immunotherapy. In a murine model of allergic asthma, HMSNs effectively delivered house dust mite allergens, reducing eosinophil infiltration, serum IgE levels, and Th2 cytokine production. These results highlight their potential to modulate immune responses and alleviate airway inflammation [91].

Table 1 provides a summary of key MSN platforms, highlighting their particle sizes, therapeutic payloads, and corresponding biological outcomes.

Table 1. Summary of Key MSN Platforms: Particle Size, Payloads, and Therapeutic Outcomes.

MSN Type / Surface	Particle Size (nm)	Payload Type	Disease Model / Application	Key Therapeutic Outcome	Study (Ref)
CD44-targeted MSN	~50	Anti-inflammatory drug	IBD	Mucosal healing, ↓ cytokines	[46]
Radial MSN (RMSN)	~510	Dexamethasone	Rheumatoid arthritis	Joint recovery, ↓ swelling	[50]
H_2-releasing MSN	220	Ammonia borane	Spinal cord injury	Microglial polarization, tissue	[53]

				repair	
Gated MSN	~200	Dexamethasone	Acute lung injury	↓ pulmonary inflammation	[61]
MSN vaccine carrier	100–200	Monkeypox antigens	Viral vaccine	↑ IgG, ↑ IFN-γ	[70]
Dendritic MSN	~200	SARS-CoV-2 RBD + T-cell epitope	COVID-19 vaccine	↑ neutralizing antibodies, T-cell activation	[71]
HMSN (large pore)	~150	Ovalbumin + CpG	Cancer vaccine	↑ CTL response, tumor suppression	[81]
HMSN allergen carrier	~100	Dust mite allergen	Allergy immunotherapy	↓ Th2 cytokines, ↓ eosinophil infiltration	[91]
MSN adjuvant	~40	Schistosoma antigen	Parasitic vaccine	↑ dendritic activation, ↑ cytokines	[80]

A comparative Efficacy summary of outcomes achieved by MSN-based platforms across various disease models is presented in Table 2.

Table 2. Comparative Efficacy of MSN-Based Therapeutics Across Disease Models.

Disease Model	**MSN Strategy**	**Key Outcome**	**Ref.**
Inflammatory Bowel Disease	CD44-targeted pH-responsive MSNs	Mucosal healing, cytokine reduction	[46]
Colitis	Dual scavenger MON-PEI system	cfDNA and ROS clearance, ↓ inflammation	[47]
Rheumatoid Arthritis	Dex-loaded RMSNs	Joint recovery, reduced swelling	[50]
Osteoarthritis	Lubricating bMSNs	Improved lubrication, ↓ joint damage	[51]
Parkinson's Disease	EGCG + MCC950 co-delivery via MSNs	Motor improvement, ↓ neuroinflammation	[52]
Spinal Cord Injury	H_2-releasing MSNs	Microglial polarization, tissue repair	[53]
Acute Lung Injury	Dex-loaded gated MSNs	↓ pulmonary inflammation	[61]
Abdominal Aortic Aneurysm	Targeted anti-inflammatory MSNs	↓ cytokines, vascular stabilization	[57]
Myocardial Infarction	MSN–neutrophil apoptotic body hybrid	Macrophage efferocytosis, cardiac repair	[58]
Skin Inflammation	Etoricoxib-loaded MSN gel	Enhanced transdermal delivery, ↓ inflammation	[59]
Bone	Pollen-like MSNs (PMSNs)	Osteoimmune modulation, bone healing	[60]

Regeneration			
General Inflammation	Caffeine-loaded MSNs (CSNPs)	↓ COX-2 and TNF-α, improved biocompatibility	[64]

Challenges and Limitations

Mesoporous silica nanoparticles (MSNs) offer high drug loading, tunable release, and targeted delivery, making them attractive for cancer immunotherapy [18]. However, several barriers hinder their clinical translation. Potential toxicity—linked to particle size, morphology, and surface charge—can lead to inflammation, oxidative stress, and organ-specific damage, especially in the liver and kidneys [92]. Although coatings like chitosan reduce toxicity, PEGylation may worsen vascular conditions [93]. Rapid clearance by the reticuloendothelial system (RES) lowers MSN accumulation at tumor sites, requiring higher doses and raising systemic risks [17]. Their slow biodegradation and tissue persistence also pose long-term safety concerns, despite efforts to improve breakdown via metal doping or hybrid designs [96]. The tumor microenvironment (TME)—with its acidity, hypoxia, and immune suppression—further complicates MSN performance, and stimuli-responsive designs remain unpredictable in vivo [17,94]. Immunotoxicity is another concern, as MSNs may unintentionally activate or suppress immune cells depending on their surface properties and dosage [95]. Manufacturing challenges—such as batch variability in size and surface features—affect reproducibility and regulatory compliance [96]. Clinical translation is slowed by limited trial data, lack of standardized evaluation methods, and insufficient biomarkers [97]. Environmental and ethical issues also arise, including the unknown ecological impact of MSN disposal and potential bioaccumulation [96]. Targeting efficiency is often compromised by protein corona formation, reducing therapeutic precision and increasing side effects [95]. Finally, integrating MSNs with combination therapies such as photothermal, photodynamic, or checkpoint blockade treatments increases system complexity and may introduce new safety concerns. Multifunctional platforms must be carefully designed to balance efficacy with biocompatibility [21].

Future Directions and Recommendations

Next-generation MSNs are being designed with multi-responsive capabilities, enabling precise, site-specific drug release in complex biological environments. These smart systems respond to internal triggers like pH, enzymes, and redox conditions, as well as external stimuli such as light and magnetic fields. Polymer-functionalized MSNs show strong potential for minimizing off-target effects [98], while dual- and multi-stimuli-responsive designs help overcome tumor heterogeneity [99]. Hybrid platforms combining MSNs with materials, quantum dots, or gold nanoparticles offer

multifunctionality, integrating imaging, photothermal therapy, and magnetic guidance. pH-responsive polymer-coated hybrids have demonstrated controlled release and improved biocompatibility, ideal for theranostic applications [100,101]. A promising frontier is personalized cancer vaccines using MSN carriers for tumor-specific antigens or mRNA. To translate these innovations clinically, challenges like scalability, biosafety, and regulatory approval must be addressed.

Conclusion

MSNs have demonstrated exceptional versatility and promise as immunomodulatory platforms across a wide spectrum of biomedical applications, including cancer immunotherapy, treatment of inflammatory diseases, and vaccine development. Their tunable physicochemical parameters, including surface chemistry, pore size, and responsiveness to biological stimuli, enable accurate modulation of drug and antigen delivery, while their biocompatibility and structural adaptability support integration with diverse therapeutic modalities. In cancer immunotherapy, MSNs have been successfully engineered to deliver tumor antigens, immune checkpoint inhibitors, and adjuvants, enhancing dendritic cell activation and cytotoxic T-cell responses. Multifunctional MSN-based systems combining photothermal, photodynamic, and chemo-immunotherapeutic strategies have shown synergistic effects and improved survival in preclinical models. Similarly, in inflammatory diseases, MSNs facilitate targeted delivery of anti-inflammatory agents and enable modulation of immune cell behavior, offering promising avenues for treating autoimmune and neurodegenerative conditions. As vaccine carriers and adjuvants, MSNs improve antigen stability, uptake, and presentation, leading to stronger and more durable immune responses. Their ability to co-deliver antigens and immunostimulatory molecules positions them as next-generation platforms for both human and veterinary vaccines, including those targeting emerging pathogens. Despite the significant advances made in this field, there are still several challenges that need to be addressed. These include the accelerated clearance of drugs by the reticuloendothelial system, potential toxicity at high doses, and limited clinical validation. Addressing these issues through smart design, hybridization with other nanomaterials, and personalized approaches will be critical for translating MSN-based therapies into clinical practice. In conclusion, MSNs represent a powerful and adaptable nanotechnology for immunomodulation. With continued interdisciplinary research and refinement, they are poised to play a transformative role in precision medicine, enabling safer, more effective, and personalized treatments for complex immune-mediated diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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