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REVIEW

Drug delivery systems based on mesoporous silica nanoparticles for the management of hepatic diseases

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Abstract The liver performs multiple life-sustaining functions. Hepatic diseases, including hepatitis, cirrhosis, and hepatoma, pose significant health and economic burdens globally. Along with the advances in nanotechnology, mesoporous silica nanoparticles (MSNs) exhibiting diversiform size and shape, distinct morphological properties, and favorable physico-chemical features have become an ideal choice for drug delivery systems and inspire alternative thinking for the management of hepatic diseases. Initially, we introduce the physiological structure of the liver and highlight its intrinsic cell types and correlative functions. Next, we detail the synthesis methods and physicochemical properties of MSNs and their capacity for controlled drug loading and release. Particularly, we discuss the interactions between liver and MSNs with respect to the passive targeting mechanisms of MSNs within the liver by adjusting their particle size, pore diameter, surface charge, hydrophobicity/hydrophilicity, and surface functionalization. Subsequently, we emphasize the role of MSNs in regulating liver pathophysiology, exploring their value in addressing liver pathological states, such as tumors and inflammation, combined

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with multi-functional designs and intelligent modes to enhance drug targeting and minimize side effects. Lastly, we put forward the problems, challenges, opportunities, as well as clinical translational issues faced by MSNs in the management of liver diseases.

1. Introduction

The liver, as the largest visceral organ in the human body, located in the upper right side of the abdomen, not only serves as the main metabolic center but is also the richest organ in the reticuloendothelial system (RES). It performs multiple life-sustaining functions, including detoxification, transforming toxins into harmless substances or forms easily excreted from the body; metabolic regulation, involving the metabolism of carbohydrates, fats, and proteins, regulating blood sugar levels, and synthesizing bile acids; substance storage, storing vitamins and minerals as well as glycogen; blood purification and filtration, producing bile to aid in the digestion of fats and clearing waste from the body. During these processes, diversiform cell types, including hepatocytes, cholangiocytes, hepatic stellate cells (HSC), Kupffer cells (KC), and liver sinusoidal endothelial cells (LSEC), collectively regulate the liver's physiological functions[1]. To be specific, hepatocytes, as the liver's primary epithelial cell group, carry out the majority of metabolic functions. Cholangiocytes are involved in the formation and secretion of bile, acting as cells within the bile duct lumen. HSC stores vitamin A in a quiescent state and participates in the liver's repair and fibrosis process upon activation due to liver damage. KC, as the liver's resident macrophages, are responsible for identifying and eliminating foreign substances in the blood, including nanoparticles (NPs). LSEC, with their unique fenestrated structure, are crucial for the exchange of materials between plasma and liver, making the liver a primary metabolic site for NPs[2].

Liver diseases, including hepatitis, cirrhosis, and liver cancer, among others, cause the deaths of over 2 million people worldwide each year, responsible for 4% of all global mortality cases and posing a significant health and economic burden globally[3]. To our knowledge, liver diseases essentially begin with hepatitis and gradually transition to cirrhosis or liver cancer. Major causes of cirrhosis include infection with the hepatitis B virus (HBV) and hepatitis C virus (HCV), alcohol-related liver disease, and non-alcoholic fatty liver disease (NAFLD)[4,5]. Inflammatory response is a common pathway for many liver diseases, while pathogenesis and pathological changes in different etiologies are still distinct. Key risk factors (such as viruses, alcohol, poisons, etc.) induce an inflammatory response and continue to damage hepatocytes, resulting in hepatocyte regeneration and diffuse fibrosis, destroying the normal structure of hepatic lobules and replacing them with fiber-wrapped hepatocyte nodules (pseudobulbs) in the liver, which are typical pathophysiological manifestations of cirrhosis. These causes may also induce liver cancer, especially hepatocellular carcinoma (HCC), as the sixth most common cancer globally and the third leading cause of cancer death. In the field of liver cancer treatment, chemotherapy remains the most widely used treatment method[6]. Treating liver diseases, especially hepatitis and liver cancer, is crucial for alleviating the enormous economic burden of liver diseases and improving patient quality of life. Therefore, a major priority in medical research is to develop nano-drug delivery systems (Nano-DDS) to improve effectiveness, achieve targeting, and minimize the side effects of drugs for the treatment of hepatic diseases.

Mesoporous silica NPs (MSNs) with pore sizes between 2 and 50 nm were initially developed by the Mobil Oil research team in 1992 through the M41S project and have become a focus in biomedicine fields. Compared to organic "soft" nanocarriers (*e.g.*, liposomes, lipid NPs, micelles, etc.), inorganic mesoporous silica NPs (MSNs) offer diversiform sizes and shapes, distinct morphological properties and favorable physico-chemical features, making them an ideal choice for controlled drug and gene delivery systems[7]. The developed pore networks adsorb a large number of therapeutic agents, improve the solubility of drugs, and effectively regulate the drug loading and release kinetics (such as rapid release and sustained release) according to the characteristics of drugs. Additionally, nanosized MSNs display biological advantages, which can be phagocytic and ingested by cells. By rational design on the size, shape, and pore features of MSNs, as well as surface modifying with functional groups, sensitive moieties, and specific ligands, researchers have developed stimuli-responsive, target, and/or intelligent Nano-DDS to improve the bioavailability and therapeutic efficacy and minimize the unwanted side effects. Concurrently, owing to its unique cellular composition and rich blood supply, the liver plays a crucial role in the metabolism and biotransformation of NPs, enclosing MSNs. NPs are transported to the liver through the bloodstream. They are recognized and processed by various liver cells, where hepatocytes are responsible for the uptake and decomposition of NPs, while KC participates in the engulfment and clearance of NPs[4]. Furthermore, HSCs are activated in response to liver damage induced by NPs and take part in subsequent repair processes. LSEC facilitates the exchange of materials between NPs and liver cells, affecting the biological fate of NPs.

This review aims to summarize the application scenarios and clinical significance of MSNs in the treatment of liver diseases. Initially, we introduce the physiological structure and function of the liver and highlight its intrinsic cell types. Next, we detail the synthesis methods and physicochemical properties of MSNs and their ability to control drug loading and release. Particularly, we discuss the interactions between liver and MSNs with respect to the passive targeting mechanisms of MSNs within the liver by adjusting their particle size, pore size, surface charge, hydrophobicity/hydrophilicity, and surface functionalization. Most importantly, we emphasize the role of MSNs in regulating liver pathophysiology, exploring their value in addressing liver pathological states, such as tumors and inflammation, combined with multi-functional design and intelligent modes to enhance drug targeting and minimize side effects. Lastly, we put forward the problems, challenges, opportunities, as well as clinical

translational issues faced by MSNs in the management of liver diseases.

2. Physiological structure and function of the liver

2.1. Liver structure

The liver is a vital organ located in the upper right quadrant of the abdomen, weighs about 1.4 kg in an average adult, and beneath the diaphragm and above the stomach, right kidney, and intestines. It is divided into two primary lobes: the larger right lobe and the smaller left lobe, separated by the falciform ligament (Fig. 1A). The lobe is made up of smaller units called lobules, which consist of hepatocytes arranged in plates radiating outward from a central vein and serves as functional units of the liver[5]. The spaces between these plates are known as sinusoids, through which blood from the hepatic artery and portal vein flows. Sinusoids are lined with endothelial cells and KC, the latter being specialized macrophages that remove debris and pathogens from the blood. At the corners of each lobule are portal triads, which consist of a branch of the hepatic artery, a branch of the portal vein, and a bile duct. The hepatic artery supplies oxygen-rich blood to the liver, while the portal vein carries nutrient-rich blood from the gastrointestinal tract. The bile ducts collect bile produced by hepatocytes, transport it to the gallbladder for storage and concentration, and eventually to the duodenum for digestion[7]. The liver's unique dual blood supply, comprising both oxygenated blood from the hepatic artery and nutrient-rich blood from the portal vein, is essential for its diverse functions, including metabolism, detoxification, and bile production[8].

2.2. Liver functions

2.2.1. Liver metabolism and biotransformation

The liver is a central organ in both metabolism and detoxification, responsible for processing carbohydrates, lipids, proteins, and other small molecules. It helps regulate blood glucose levels by storing glucose as glycogen after meals, with enzymes like glycogen synthase ensuring stable glucose levels and overall energy balance[9,10]. In lipid metabolism, the liver synthesizes, breaks down, and transports fats while also producing bile acids and plasma lipoproteins to maintain lipid homeostasis[9]. Disruptions in these pathways can lead to conditions such as fatty liver disease, obesity, type 2 diabetes, and cardiovascular disorders. Additionally, the liver breaks down amino acids and converts dietary proteins into amino acids for protein synthesis and distribution throughout the body. The liver is also involved in metabolizing hormones and drugs, ensuring they function safely and effectively. In its detoxification role, the liver processes toxins and drugs through biotransformation, which occurs in two stages. The first stage involves oxidation, reduction, or hydrolysis, increasing water solubility[11]. The second stage involves binding these compounds to molecules like glutathione or glucuronic acid, further enhancing water solubility for easier excretion[12]. Liver damage can impair these processes, highlighting the importance of liver health for effective detoxification.

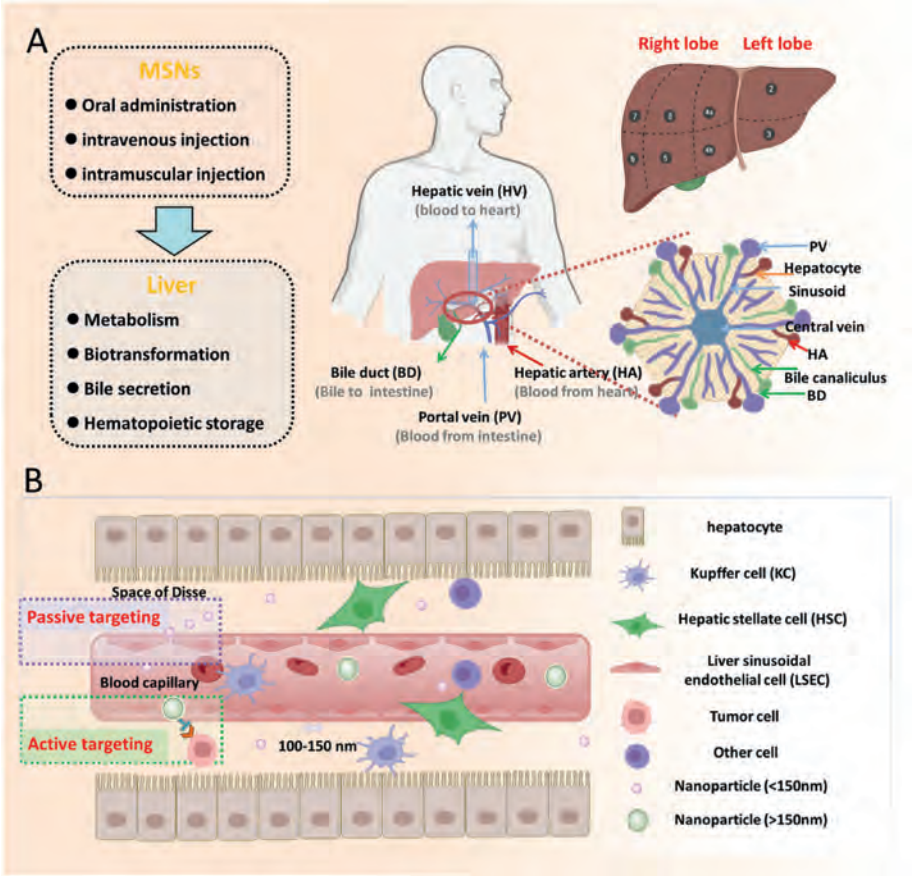

Figure 1 Structure and function of the liver. (A) Macrostructure and function of the liver. (B) Microstructure and typical cell types in the liver.

2.3. Hepatocyte types and functions

Fig. 1A highlights the organization within a hepatic lobule, including the portal vein that brings nutrient-rich blood from the gastrointestinal tract. This central vein drains blood from the lobule, the hepatic artery that supplies oxygen-rich blood, and the bile ducts and canaliculi involved in bile secretion and transport. The complex physiological structure and function of the liver benefit from the close cooperation of multiple cell types (Fig. 1B). These include hepatocytes, which are the main functional cells of the liver responsible for metabolic processes; HSCs, which are involved in vitamin A storage and liver fibrosis; KC, acting as macrophages to break down red blood cells and combat infections; fibroblasts, which produce extracellular matrix (ECM) and collagen; and LSEC, which line the liver sinusoids. Additionally, the hepatic microenvironment consists of various immune cells, such as B cells, T cells, and natural killer (NK) cells, playing substantial roles in the liver's immune response. The intricate interplay between these cells and structures is crucial for maintaining liver function and homeostasis.

2.3.1. Hepatocytes

Hepatocytes, account for the most cells in the liver, perform key biological functions, including the regulation of glucose, amino acid, lipid, and fat metabolism, and manage energy storage and supply through glycogen synthesis and glycolysis[13]. Hepatocytes purify blood by transforming harmful substances such as drugs, alcohol, and toxins into harmless ones and excreting them through bile or urine, maintaining the stability of the body's environment. They are also involved in protein synthesis, such as producing clotting factors to ensure effective blood clotting, thereby preventing abnormal bleeding. Additionally, hepatocytes store glycogen, vitamins, and trace elements, maintaining basic nutritional balance. They have an immune function by presenting antigens to activate immune cells and ensure the body's protective mechanisms.

Fortunately, hepatocytes have a strong ability to regenerate and can proliferate rapidly to repair the damaged tissue once the liver is injured. However, excessive injury or pathological condition may lead to liver fibrosis, which is a pathological change caused by excessive activation of HSC, and eventually lead to liver cirrhosis[14,15].

2.3.2. KC

KC is a kind of specialized fixed macrophage, mainly distributed in the inner wall of hepatic sinusoids, with the function of immune surveillance, pathogen phagocytosis, and scrap clearance. They are involved in the regulation of liver inflammation. When the liver is injured or infected, it first identifies and engulfs pathogens or danger signals in the blood, such as bacteria, viruses, and parasites. It then destroys them by phagocytosis and decomposition. Meanwhile, they release a variety of immunomodulatory factors, such as cytokines and chemokines, to activate and guide other immune cells to participate in the immune response and enhance the body's resistance. They are also responsible for phagocytosis and the removal of dead or damaged cells, including dead hepatocytes, which are very important for maintaining the homeostasis of liver tissue.

2.3.3. HSC

HSCs, as specialized cells located between LSEC and the hepatic interlobular septum (Disse's space), are crucial in liver health and disease progression. In a normal state, they store vitamin A and help maintain liver stability. In a pathological state, they promote liver fibrosis[16], making them important targets for studying liver disease mechanisms and developing anti-fibrosis treatments[17]. This activation causes them to lose their vitamin A storage capability and express smooth muscle actin (α-SMA) as a marker of cell activation. They produce collagen and other ECM, leading to structural damage and liver dysfunction, driving hepatic fibrosis and cirrhosis. HSCs also attract and interact with immune cells by secreting various cytokines and chemokines, further promoting inflammation and fibrosis[18]. Additionally, activated HSCs can cause hepatic sinusoid contraction, regulating blood flow into the liver, which may contribute to portal hypertension, a common complication in liver cirrhosis.

2.3.4. Hepatoma cells

Hepatoma cells are malignant tumor cells in the liver, and the most common is hepatocellular carcinoma (HCC) derived from hepatocytes. They lose the typical functions of normal hepatocytes and gain uncontrolled proliferation, avoiding programmed cell death (apoptosis) and invading other tissues[9]. The development of hepatocellular carcinoma is influenced by factors such as genetic mutations, cell signal pathway imbalances, abnormal cell cycle regulation, epigenetic changes, and microenvironment alterations[10]. Hepatoma cells regulate energy sources (*e.g.*, increasing glycolysis for rapid energy), create conditions conducive to tumor growth, and spread by secreting growth factors, cytokines, and other signaling molecules[19]. They also have immune escape capabilities, affecting the host's immune system to reduce surveillance and response. Their high genetic and epigenetic heterogeneity means significant differences can exist between cancer cells within the same tumor, complicating treatment and leading to varied responses, treatment failure, and disease recurrence[20]. Their invasiveness and metastatic ability allow them to spread to other organs (*e.g.*, lungs, bones, brain) through the blood or lymphatic system, complicating treatment further.

3. MSNs for controlled drug loading and release

3.1. Synthesis and properties of MSNs

Since MCM41 was first discovered in the early 1990s, MSNs have brought new possibilities and discovered widespread applications because of their ease of synthesis and beneficial physical and chemical characteristics[4,11,12,21]. The synthesis of MSNs comprises several distinct methods, including the sol-gel method, microemulsion method, soft-template method, hard-template method, etc. The sol-gel method, particularly *via* the Stöber process[22], is central to MSN synthesis. In alkaline conditions, surfactants like CTAB and CTAC or triblock copolymers such as Pluronic F127 facilitate the production of MSNs through a base-catalyzed mechanism, where hydrolysis and condensation are involved as key steps[23,24]. What's more, the Henderson−Hasselbalch equation plays a crucial role in this process by linking the concentrations of silanol and silanolate to the pH level and p*K*a value[25]. The microemulsion method, in contrast, advances MSN synthesis by allowing precise control over particle morphology. This technique involves forming a water-in-oil microemulsion where surfactants like CTAB create micelles acting as nanosized reactors, adding silica source to these micelles and resulting in silica formation[26,27], by adjusting the surfactant amount, oil-to-water ratio, and precursor concentration, the size, shape, and structure of the NPs can be controlled. The soft-template method

utilizes amphiphilic molecules, such as nonionic surfactants, to form specific microstructures through self-assembly. These surfactants guide the deposition and assembly of silica sources like tetraethyl orthosilicate (TEOS), which undergo hydrolysis and condensation within the formed liquid crystalline phases. The surfactant template was then removed by calcination or ethanol washes, yielding pure MSNs with uniform size, large surface areas, and excellent thermal stability[28,29]. The hard-template method employs rigid preformed templates, such as SBA-15 or carbon nanotubes, to create well-defined mesostructures[30]. Silica precursors like TEOS are uniformly applied to these templates *via* impregnation and chemical vapor deposition. The silica precursor undergoes a sol-gel process[31], leading to silica formation within the pores or on the template surface with precise control over pore size and shape. This method is vital for applications in catalysis, drug delivery, and adsorption, offering enhanced physicochemical properties and controlled mesostructures.

In addition to the above classic MSN synthesis methods, researchers endow morphological and structural diversities of MSNs by exquisite manipulation of their synthetic strategy. For example, to make full use of the interior space in MSNs, researchers first applied polymers such as polyvinylpyrrolidone (PVP), azodiisobutyronitrile (AIBN), or polystyrene (PS) to form nanospheres, allowing the hydrolysis reaction of TEOS to coat the nanospheres with SiO_2 to form a core-shell structure, and finally removed the nuclear layer to obtain Hollow MSN (HMSN) (Fig. 2A)[32]. Besides, organic expanding agents were added to improve the size of hydrophobic nuclei in micelles to obtain MSNs with enlarged pore size (Fig. 2B)[33], Jin and Yuan[34] utilized biomimetic synthesis methods using biological matrices as templates. They employed a star-shaped polyethyleneimine (sPEI4-200) with a benzene core as a template for the biomimetic synthesis of MSNs. By adjusting polymer concentrations, methanol, and TSPP (tetrakis(4-sulfonyl phenyl)porphyrin) additives, the silica can be controlled into forms. The distinctive features of this synthesis method lie in its mild reaction conditions, typically conducted at moderate temperatures and pH levels without the need for extreme chemical environments, and rapid synthesis, with the ability to control the morphology of the NPs (such as size and shape) by adjusting the reaction conditions[34,35]. Wang et al.[36] employed a novel single-micelle epitaxial growth method with an ordered template to guide material deposition to synthesize virus-like MSNs (VSN) (Fig. 2D)[36]. This method involved an oil/water biphasic reaction system, with CTAB serving as the structural template and TEOS as the silica precursor; epitaxial growth facilitated the formation of mesoporous silica cores and radially oriented silica nanotubes. Along with the substantial development in material science and computational chemistry, growing numbers of special-shaped MSNs emerge, including chiral/spiral-shaped MSNs[37–40], Janus MSNs[41], dendritic MSNs nanotrees[42], coated MSNs nanorods (CMSNR)[43], sperm-like MSNs (Fig. 2C)[44], etc., bringing great potential for their biomedical applications.

3.2. MSNs for drug loading and release

As illustrated in Fig. 3A and B, MSNs exhibit several critical characteristics, including diversiform morphology, regular shape, uniformed size, large surface area, tunable pore size, variable surface charge, ease of surface modification, and good biocompatibility capacity, which are attributed collectively to their various biomedical applications, are considered as excellent candidates in the field of drug delivery[21]. Firstly, the large surface area and pore volume of MSNs offer abundant space for drug adsorption and loading. Drug molecules are usually loaded on MSN by adsorption, and the interactions between drug molecules and the NPs mainly include hydrogen bonding and electrostatic interactions. Secondly, the delicate mesoporous structure and tunable pore size provide better control over the drug loading and release dynamics. The adsorption of cargo onto MSNs, as well as the drug loading amount, is mainly governed by the pore size and surface area, as it affects the drug diffusion to the delivery medium. Smaller pores provide greater encapsulation, thereby slowing down diffusion and release rates, while larger pores facilitate faster diffusion and release. Manzano and Vallet-Regí[45] compared MCM-41 type MSNs with pore sizes of 3.9 nm to those with 2.3 nm and found that the former released ibuprofen more quickly. Thus, scientists have strived to create MSNs *via* co-templating methods, which involves combining surfactants or adding swelling agents (such as trimethylbenzene) to surfactant solution to increase the size of the micelles, and thereafter the pore size in the final silica structure[46]. Thirdly, the non-toxic nature and favorable biocompatibility of MSNs enable their biomedical application and meanwhile minimize the toxic-side effects. For example, Trewyn et al.[47] observed that smaller particle sizes favored cellular uptake and enhanced drug delivery efficacy, while larger pores can accommodate greater volumes of therapeutic agents, affecting the drug release profile.

3.3. Functionalized design of Nano-DDS based on MSNs

In therapy, MSNs have been used to encapsulate and protect drug molecules. This ensures safe passage through the body and release at the desired sites, thereby increasing treatment efficacy and minimizing damage to healthy cells[9]. However, the real innovation lies in the ability to modify these pores to achieve controlled drug release[48]. To address this challenge, scientists have introduced stimulus-responsive caps on the mesopores, designed to respond to specific triggers in the liver microenvironment. These caps, often referred to as gatekeepers[49,50], are usually polymers or nano-entities[51] that react to specific stimuli, thereby regulating the timing and location of the encapsulated drug's release. These stimuli can be internal, such as changes in pH, temperature, or enzyme levels related to specific disease states, or external, such as magnetic fields, ultrasound, or light[51,52]. Apart from stimulus-responsive control, the functionalization of MSNs can also be tailored to achieve passive, sustained release characteristics[53], which is particularly important for maintaining long-term therapeutic levels of a drug. By adjusting the pore size, surface chemistry, and degree of functionalization, the rate of drug diffuses from MSNs can be controlled[54]; combining these two methods results in a slow and steady release, which is beneficial for maintaining a consistent drug concentration in the target area, improving therapeutic effects, and reducing the frequency of dosing. Additionally, their easily modified exterior and interior surface could functionalize with magnetic and luminescent compounds to allow *in vivo* real-time monitoring and simultaneous drug delivery, underscoring their potential in diagnostics and theranostic applications.

4. Manipulation on the MSNs–liver interactions

4.1. Passive targeting mechanisms of MSNs to the liver

Passive targeting in the liver mainly results from the anatomical structure of the liver as the primary site for the accumulation of

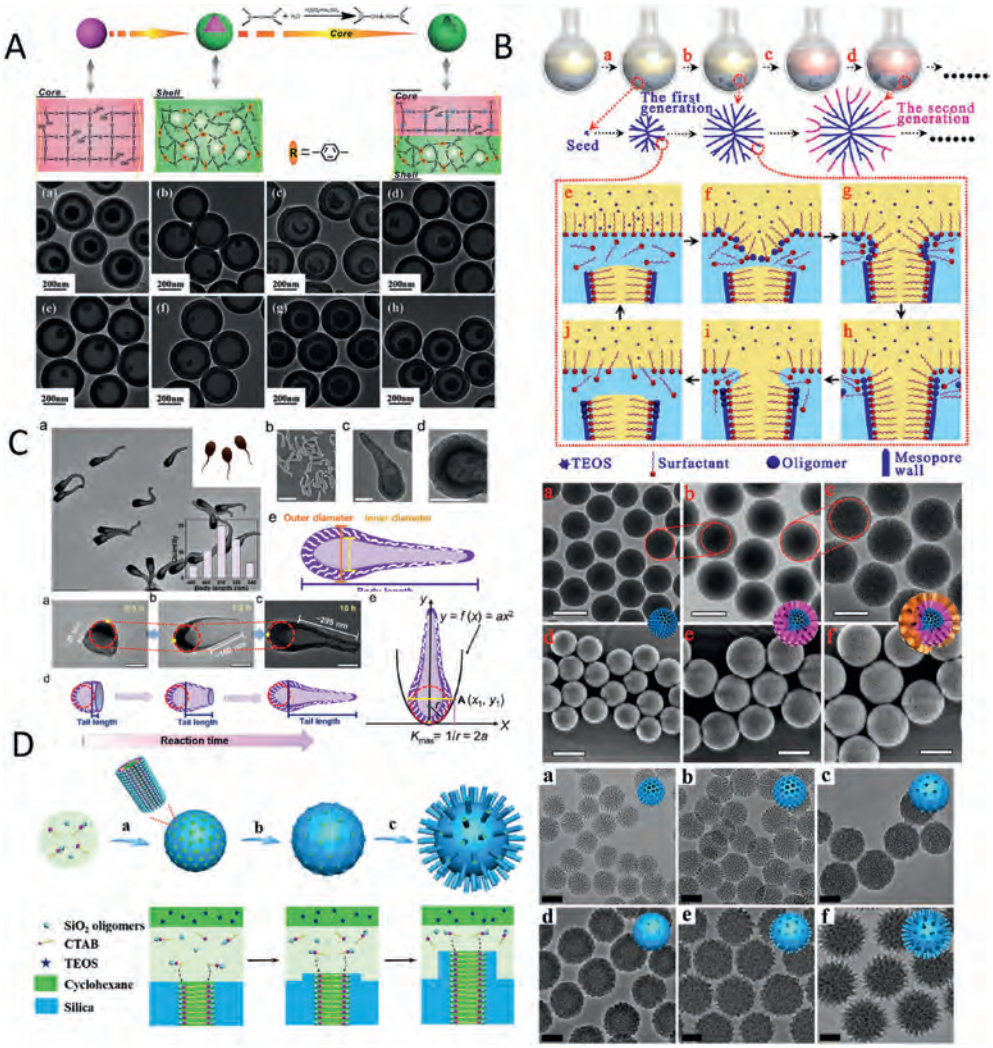

Figure 2 Advanced Synthesis of MSNs with distinct structural features. Synthetic strategy and morphology of (A) HMSN; Reprinted with the permission from Ref. 32. Copyright © 2015 Royal Society of Chemistry. (B) MSNs with enlarged pore size; Reprinted with the permission from Ref. 33. Copyright © 2014 American Chemical Society. (C) Sperm-like MSNs; Reprinted with the permission from Ref. 44. Copyright © 2021 American Chemical Society. (D) VSN; Reprinted with the permission from Ref. 36. Copyright © 2017 American Chemical Society.

various particles, including NPs[55]. This ability is not merely a passive function of its anatomical location. It also involves the complex interaction of selectively regulating the uptake, processing[56], and clearance of various molecules, where hepatocytes, KC, and other specialized cells are involved in these processes. KC participates in the engulfment and clearance of NPs. HSCs are activated in response to liver damage induced by NPs, and the subsequent repair processes. LSEC facilitates the exchange of materials between NPs and liver cells, affecting the metabolic fate of NPs.

Particularly, as the main passive targeting organ, the liver plays a critical role in the metabolism and clearance of NPs, including MSNs. Understanding the MSNs−liver interactions in view of adjusting the particle size, pore size, surface charge, and hydrophobicity/hydrophilicity of NPs is essential for optimizing NP-based therapies. MSNs in specific sizes will be preferentially absorbed by the liver, utilizing the organ's natural filtration mechanism. The regulation of surface charge on MSNs is another important method, as positively charged MSNs are usually more readily internalized by hepatocytes due to electrostatic interactions[57]. Furthermore, the liver processes hydrophilic and hydrophobic substances in different ways. The balance on the surface properties of MSNs can be exploited to optimize the interaction of MSNs with hepatocytes. In addition, surface functionalization of MSNs by attaching specific ligands or molecules to the surface of NPs, opens new pathways for targeting the liver.

4.2. MSNs−liver interactions for liver targeting

4.2.1. Adjustment of particle size and pore size

The natural and passive targeting mechanisms of MSNs in the liver are largely affected by their particle and pore sizes[58,59]. Firstly, the size of MSNs determines their circulation time, biological distribution, and targeting mechanism to the liver. Smaller particles tend to remain longer in circulation. In comparison, larger particles are more easily filtered by the liver, enhancing hepatic function, as NPs of specific sizes are pre-emptively taken up through the organ's natural filtration mechanism. NPs in the 10−200 nm range are particularly effective for biomedical applications as they can efficiently traverse biological barriers, ensuring optimal interaction with target cells and tissues[60,61].

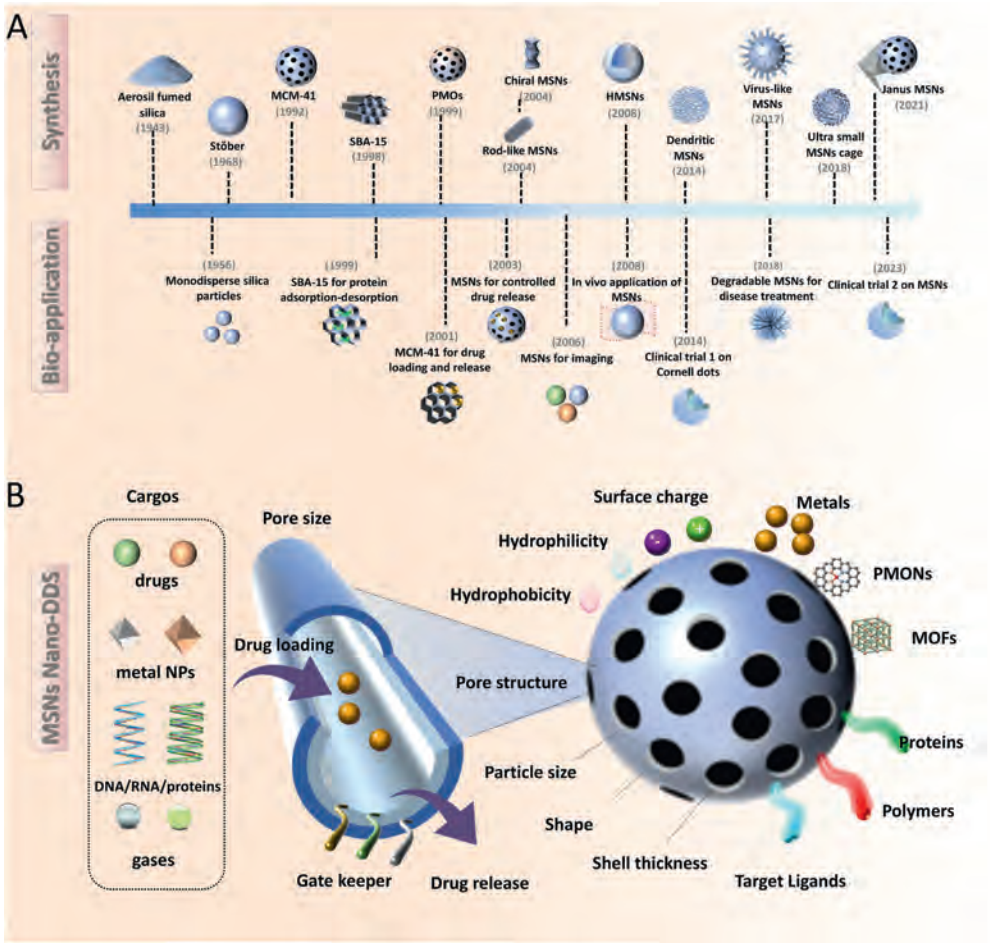

Figure 3 Synthesis, biomedical applications of MSNs and MSNs-based Nano-DDS.

Although MSNs in various sizes are primarily concentrated in the liver and spleen, they exhibit different distribution trends on account of the balance between uptake and excretion[62]. MSNs smaller than 100 nm can achieve passive targeting through the enhanced permeability and retention (EPR) effect, avoiding splenic clearance. In comparison, very small MSNs (<10 nm) are rapidly cleared by the kidneys, and larger NPs (>200 nm) are absorbed by macrophages, limiting their bioavailability[63]. Lu et al.[64] measured the uptake of fluorescein isothiocyanate-dyed MSNs (FITC-MSNs) with particle sizes of 170, 110, 50, and 30 nm by HeLa cells. After fusion with cells, FITC-MSNs were internalized, and the absorption of 50 nm FITC-MSNs was approximately 2.5-, 4-, 20-, and 11-times higher than that of 30, 110, 170, and 280 nm NPs, respectively.

The pore size of MSNs is also of great importance in determining their biological distribution, cellular uptake, and *in vivo* clearance[65]. Theoretically, MSNs of specific pore sizes utilize the natural filtration mechanism of organs and are preferentially absorbed by the liver. Li et al.[65] found that doxorubicin-loaded MSNs (DOX/MSNs) with a pore size of 5.4 nm had higher cellular uptake and DOX nucleic acid concentration in specific cells, effectively inducing cell apoptosis and anti-proliferation compared to MSNs with pore sizes of 8.2 and 2.3 nm. By controlling the pore size, the drug release rate can also be adjusted to align with the liver's metabolic processes[54]. This synchronization ensures that drug release coincides with the liver's natural rhythms, thereby enhancing the drug's effectiveness while minimizing systemic side effects[66].

4.2.2. Regulation of surface charge

Modulating the surface charge of MSNs represents a novel approach to controlling their targeting mechanisms in the liver[67,68]. The impact of surface charge extends beyond biodistribution and pharmacokinetics to broader aspects like cellular uptake. Once attached to the cell membrane, MSNs are internalized through endocytosis, with positively charged MSNs usually internalized more effectively than negatively charged or neutral MSNs[57]. Following these targeting principles, scientists have prepared more MSNs with positive charges. For example, Wei et al.[69] modified SBA-15 with azides to enable "click" functionality, followed by the Arbuzov[68] reaction to add phosphonate groups and finally introduced positive charges through quaternization with ethyl bromide. It exhibited high selectivity and rapid kinetics for uranium (VI) adsorption, attributed to electrostatic interactions between negatively charged uranium complexes and positively charged functionalized silica.

Different types of liver cells exhibit varied affinities for charged particles. Hepatocytes tend to absorb positively charged NPs owing to their negatively charged membranes. In contrast, KC preferentially uptake negatively charged ones as part of their role in clearing pathogens and debris. Reversing the surface charge of NPs also plays a crucial role in endosomal escape after

entering hepatocytes. For instance, MSNs covered with charge-reversible PAH-Cit and cationic polyelectrolyte PEI used oppositely charged polymers as gatekeepers for controlled drug release and effective endosomal escape[60]. In acidic endosomal environments, the hydrolysis of acid-cleavable bonds in PAH-Cit triggered charge reversal and endosomal escape, effectively releasing the drug[70]. Adjusting surface charge can thus enhance endosomal escape efficiency, improving the delivery and efficacy of encapsulated drugs.

4.2.3. *Alteration of hydrophilicity-hydrophobicity*

The presence of hydrophilic silanol groups on the surface of MSNs endows them with high water affinity. This characteristic directly affects the solubility, stability, and surface interface properties of NPs, thereby influencing their biodistribution and accumulation in the liver[52]. For example, Yu et al.[71] found that hydrophobic NPs adsorbed proteins 2.1 times higher than hydrophilic ones, thus showing a higher protein exchange rate. Post-synthesis modification involving grafting organosilane molecules onto the silica surface remodels the surface of MSNs to exhibit controlled hydrophobic characteristics. Leal et al.[72] modified the surface of bacterial cellulose (BC) by combining oxygen plasma deposition with trichloromethyl silane (TCMS) silanization, which altered surface roughness and energy, thereby maximizing the achieved hydrophobic effect. This transformation was necessary as hydrophobic drug molecules interact poorly with inherently hydrophilic silica but can be more effectively accommodated within mesopores to increase the drug loading capacity[73] and allow precise control over the release rate of hydrophobic drugs[74]. In another example, surfaces with enhanced hydrophobicity evaded opsonization, thus prolonging the systemic circulation time of NPs[75], which is a strategy crucial for improving targeting efficiency in liver tissue. Moreover, the interplay between hydrophilicity and hydrophobicity extends beyond drug release and biocompatibility, encompassing interactions with the ECM and cell membranes. Hydrophobic surface modifications facilitate the penetration of lipid-rich cell membranes and enhance cellular uptake. However, overly hydrophobic surfaces may lead to aggregation in biological environments, while extremely hydrophilic surfaces could result in rapid clearance from the bloodstream[76]. Finding the "optimal balance" between hydrophilicity and hydrophobicity is critical, which can be achieved by utilizing the assistance of silane chemistry and surface science.

4.2.4. *Surface functionalization*

The surface of MSNs is often tailored with various functional groups, enabling the binding of targeting ligands or the inclusion of stimuli-responsive elements. Targeted delivery is generally divided into active and passive targeting, with passive targeting relying on the pathological characteristics of the disease microenvironment and the nature of the Nano-DDS, leading to the effective accumulation of the drug at the site of disease lesions[55]. Fortunately, the liver has a rich RES and is the largest passively targeted organ. For example, Wang et al.[37] and Sang et al.[77] highlighted MSNs with spherical, rod, or spiral shapes, as well as smooth, rough, and virus-mimic surface topologies that always preferred to accumulate in the liver after oral administration. Benefiting from passive targeting to the liver and the EPR effect in tumor tissues, Doxil® (a PEGylated liposomal DOX), is the first US Food and Drug Administration (FDA)-approved nano-drug in 1995 also showed prolonged circulation time and enhanced accumulation in target tissues[78].

Transforming MSNs from passive Nano-DDS to active targeting in disease treatment will intelligently guide them to injured or diseased sites[79]. The active targeting process of MSNs always starts with attaching specific ligands, such as antibodies, peptides, or aptamers, to the surface of MSNs to enable their interaction with specific cell types or receptors in the liver[63]. This targeted approach can deliver higher concentrations of therapeutic agents to affected areas, enhancing treatment efficacy while reducing exposure of non-target tissues to these drugs, thus minimizing potential side effects. For example, Pan et al.[80] covalently coupled Arginylglycylaspartic acid (RGD) and transcription activator (TAT) peptides to highly dispersed MSNs for functionalization. The resulting MSNsRGD/TAT effectively delivered drugs for targeted tumor regression, demonstrating their potential in liver targeting. Besides, organotin-based metallodrug-attached MSNs were functionalized with folic acid (FA) for cancer-targeting, and *in vivo* studies demonstrated preferential accumulation of the Nano-DDS in tumor tissues with a potent reduction of tumor size. In a recent study, DOX was encapsulated into MSNs by the addition of hyaluronic acid (HA), which endowed MSNs with targeting capability. It was demonstrated to target mitochondria and preferentially deliver DOX to cancer cells efficiently.

Immune evasion is the second key aspect, accomplished by camouflaging MSNs from the immune system[81,82]. To avoid the rapid clearance of MSNs as foreign substances, "invisibility" to MSNs has been granted to achieve immune evasion[83]. For example, Chen et al.[84] reviewed that the pegylation of MSNs by attaching PEG chains to the surface provided a hydrophilic and neutral barrier, reducing the immune system's recognition and uptake. This stealthiness not only prevented opsonization and subsequent phagocytosis but also extended their circulation time in the blood, ensuring more effective targeting of the liver.

The synergistic action between functionalized MSNs and liver metabolism is another critical aspect. In this synergistic action, functionalization aims to complement the liver's natural metabolic pathways, facilitate the absorption and processing of MSNs by hepatocytes or KC, and utilize the liver's inherent biological processes to enhance the efficacy of drug delivery[85]. For instance, attaching peptides or antibodies that recognize specific liver cell markers can direct MSNs toward damaged liver tissue, ensuring the release of therapeutic drugs into the target cells[45]. These modifications in targeting and immune evasion not only enhanced the therapeutic performance of MSNs but also extended their application beyond traditional drug delivery (as shown in Table 1[60,61,68,69,79,81,82,86−122]). In another example, MSNs were used in diagnostic imaging, where their targeting nature allowed for precise visualization of liver tissue[123].

4.3. *Safety, toxicology, and biocompatibility of MSNs*

Taking into account their clinical application prospect, MSNs are generally considered biocompatible due to their inert silica composition, which is similar to natural silica found in the body. Studies have demonstrated that MSNs can be safely administered at appropriate doses without causing significant adverse effects. For example, Zhang et al.[124] found that MSNs with a supported lipid bilayer (SLB) showed high drug loading and controlled release in response to hyperthermia, reducing premature drug release and minimizing toxicity to healthy tissues. However, the toxicological profile of MSNs is influenced by factors such as particle size, surface charge, pore size, and surface functionalization. Smaller MSNs (<100 nm) can induce oxidative stress and

Table 1 MSNs-based nano-DDS with surface functionalizations.

Nanodrug name	Component	Targeting	Loading agent	Liver disease	Characteristic	Experimental model	Ref.
Gal-PDA-MSN@AspPDA	Galactosamine, polydopamine, aspirin, and MSNs	pH-sensitive and targeted	Aspirin	Liver cancer	Toxicity and inhibitory effects on liver cancer cells	Mice and HepG2	69
MSN@CM-GN3	Triantennary *N*-acetylgalactosamine-engineered cell membrane and biodegradable MSNs	Passively targeting and EPR effects	siPCSK9	Non-alcoholic fatty liver disease	Strong hepatocyte targeting, KC escaping, and good biocompatibility	HepG2, RAW264.7 cells, L929 cells, HUVECs and HFD-induced mice	68
MF@SOR	Manganese-doped MSNs, sorafenib, and MIL-100	Passively targeting and EPR effects	Sorafenib	Liver cancer	ICD inducing, dendritic cell maturation, exposure of double-stranded DNA, and activation of cGAS−STING pathway	HUVECs, Hepa1-6, JAWS II cells, and C57BL/6J mice	86
PEG-MSN@ATO	MSNs modified with amino groups, arsenic trioxide, and PEG	pH-sensitive and targeted	Arsenic trioxide	Liver cancer	Uniform size, good loading efficiency, pH-responsive release features, decreased macrophage uptake, and enhanced dendritic cell activation	Mice and HepG2	87
TSBRs	HMSN with the thioether-hybrid structure modified with glucose oxidase, oxygen, and DOX	Cancer cell membrane	DOX	Liver cancer	Spherical, excellent surface area and pore size distribution, and better cytotoxicity and inhibition of tumor size and weight	Mice and HepG2	60
COSM@MSN-NH2-GA	Three-dimensional dendritic MSNs, glycyrrhetinic acid covalently modified on MSN surfaces through amide bond and then loaded with COSM to form drug-loaded NPs	Passively targeting and EPR effects	COSM	APAP-induced liver injury	Neutral surface charge, biocompatibility, and high drug loading	LO2 cells and drug-induced liver injury model	61
HMSN-ISO@ProA-PD-L1 Ab	Isorhamnetin (ISO) and anti-PD-L1 antibody dual-functional MSNs	PD-L1 targeting	Isorhamnetin	Liver cancer	Improved tumor immune microenvironment, and inhibition of YY1-mediated tumor progression	Hepa1-6 transplanted tumors	88
NOSH@MSN-Au-Gal	Gold-capped MSNs loading NOSH-aspirin, a nitric oxide and hydrogen sulfide	Passively targeting and EPR effects	NOSH-aspirin	Liver cancer	Liver targeting and TME responsive properties, and combined gas-radiotherapy	Subcutaneous and orthotopic HCC tumors and HepG2 cells	89
HMSN@ASX	Astaxanthin-loaded HMSN	Passively targeting and EPR effects	Astaxanthin	APAP-induced liver injury	Reduced autophagy, enhanced apoptosis, targeted delivery, and activating the Nrf2/HO-1 pathway	LO2 cells and drug-induced liver injury model	90
mD@cSMN	$SiPCCl_2$-hybridized MSNs with coordination of Fe(III)-captopril, and coating with exfoliated membrane of matured DCs by H22-specific neoantigen stimulation	LNP targeting	Fe(III)-captopril	Liver cancer	Polarization of N_2 phenotype neutrophils, *in situ* tumor vaccination, achieve complete tumor regression (83%) and prolong the survival time	H22-bearing mice	91
TMSN-NH2@Epi	Redox-responsive MSNs with triantennary *N*-acetylgalactosamine cluster	Passively targeting and EPR effects	Epirubicin	Liver cancer	High affinity to asialoglycoprotein receptors overexpressed in HCC cells, suitable physicochemical properties for drug delivery, high drug loading capacity, high	HepG2 cells	92

(*continued on next page*)

Table 1 (*continued*)

Nanodrug name	Component	Targeting	Loading agent	Liver disease	Characteristic	Experimental model	Ref.
					biocompatibility, and targeting ability to HCC cells		
a-PM-S-MSNP	MSNs coated with platelet membrane (PM)	Self-amplified accumulation manner	Sorafenib	Liver cancer	Favorable anti-HCC immunity and anti-angiogenesis effect, potent anti-HCC effect, and significantly prolonged overall mice survival	Subcutaneous and orthotopic HCC tumors and HepG2 cells	93
MSNs@Pue	MSNs and puerarin	Passively targeting and EPR effects	Puerarin	Alcoholic hepatitis	ERK/mTOR signaling pathway activation	Acute-on chronic ethanol-drinking induced alcoholic hepatitis	94
ECH@AMPG	MSNs, galactose, and poly(ethylene glycol) diglycidyl ether conjugation	Passively targeting and EPR effects	Echinacoside	Liver cancer	Promoted apoptosis and inhibited glycolysis	Subcutaneous and orthotopic HCC tumors and HepG2 cells	95
HM@ISO@DOX	Hyaluronic acid-conjugated and manganese-doped MSNs, DOX, and isoginkgetin	Tumor targeting capability *via* the conjugated hyaluronic acid	DOX	Liver cancer	Biodegradation, tumor targeting, and activation of autophagy through AMPKa−ULK1 pathway and inhibition of HCC cell proliferation	Subcutaneous and orthotopic HCC tumors, HepG2 cells, and Huh7 cells	96
mSCCC@SA	Nanohybrid ($mSiO_2$/CaO_2/CPPO/Ce_6: mSCCC) NPs and stearic acid	Passively targeting and EPR effects	Chemiluminescent agent	Liver cancer	Self-supplies of H_2O_2, O_2, and Ca_2^+, CRET-mediated PDT without the use of external light, and calcium-overloaded-cell death	Subcutaneous and orthotopic HCC tumors and HepG2 cells	79
TA-MS-NH2 NPs	Amino-functionalized tannic acid-templated MSNs	Passively targeting and EPR effects	Tannic acid	Iron-induced acute liver toxicity	Improved oxidative stress markers	Wistar rats	97
AB@HMSN@PEG	HMSN, ammonia borane, and PEG coating	Passively targeting and EPR effects	Ammonia borane	Metabolic dysfunction-associated fatty liver disease	Sustained and ultrahigh H_2 supply, reduced lipid synthesis, and increased fatty acid metabolism	Diet-induced and genetic mutation induced early-stage MAFLD mice	98
IMB16-4-MSNs	MSNs and IMB16-4	Passively targeting and EPR effects	IMB16-4	Liver fibrosis	Decreasing the expression of hepatic fibrogenic markers	LX-2 cells	99
MSN@H6L@β-CD@AMPPD	3-[(2-Spiroadamatane)-4-methoxy-4-(3-phosphoryloxy)-phenyl-1,2-dioxetane] dioxetan, β-cyclodextrin, mesoporous silica loaded with (4-carboxyphenyl) porphyrin	Passively targeting and EPR effects	(4-Carboxyphenyl) porphyrin	Liver cancer	Liver cancer-targeting chemiluminescence and hydrolyzed by the liver cancer alkaline phosphatase	Subcutaneous and orthotopic HCC tumors, SMCC-7721 cells	100
TLS11a-LB@TATp-MSN/DOX	Liposomes that carried liver cancer-specific aptamer TLS11a, TAT peptide-MSN, and DOX	Passively targeting and EPR effects	DOX	Liver cancer	Deliver DOX to the nuclei of liver cancer cells by dual targeting liver cancer tissue and the nuclei of the cancer cells	Subcutaneous and orthotopic HCC tumors, SMCC-7721 cells	101
(ICG + S)@$mSiO_2$	Indocyanine green and sorafenib co-loaded MSNs	Passively targeting and EPR effects	Sorafenib	Liver cancer	Excellent fluorescence imaging ability, remarkable photothermal tumor killing effect, and immune enhancement capability	H22 tumor-bearing mice	102

miR-MSNs	MSNs and miR-33 antagomirs	Passively targeting and EPR effects	miR-33 antagomirs	Metabolic dysfunction-associated fatty liver disease	Lowered the serum triglyceride level and reduced hepatic steatosis	High-fat diet fed mice	81
SiO_2-NH_2@ICG	MSNs and indocyanine green	Passively targeting and EPR effects	Indocyanine green	Liver cancer	Efficient photothermal effects	HepG2 cells	82
MSNM@SFN	Sorafenib and MSNs	Passively targeting and EPR effects	Sorafenib	Liver cancer	Co-administrating with FFA *via* co-administration with NSAIDs	Subcutaneous and orthotopic HCC tumors and HepG2 cells	103
FA-LB-CHMSN with DM-NCTD/ABT-737	Folate receptor-targeted lipid bilayer-supported chlorodimethyloctadecylsilane-modified MSNs	FA targeting	DM-NCTD and ABT-737	Liver cancer	Apparent tumor cell apoptosis and tumor inhibition with significant cellular apoptosis in the tumor and no obvious toxicity to the tissues	H22-bearing mice	104
CIMs	CAR-T cell membranes andMSNs containing IR780 NPs	Passively targeting and EPR effects	IR780	Liver cancer	Superior targeting ability and photothermal antitumor abilities	Subcutaneous and orthotopic HCC tumors, Huh-7 cells	105
MSPLNPs	pH-low-insertion-peptide, MSNs-coated persistent luminescence NPs	Passively targeting and EPR effects	DOX	Liver cancer	Tumor target imaging without autofluorescence interference and well-defined NIR persistent luminescence performance	A549 and HepG2 cells	106
GPDC-MSNs	Galactosyl-conjugated PEO-PPO-PEO, lipid (2E)-4-(dioleostearin)-amino-4-carbonyl-2-butenonic, and antitumor drug irinotecan (CPT-11)-loaded MSNs	Lipid (2E)-4-(dioleostearin)-amino-4-carbonyl-2-butenonic	CPT-11	Liver cancer	HCC targeting, enhancing cellular internalization, achieving superior antitumor efficacy and low systemic toxicity	Subcutaneous and orthotopic HCC tumors and HepG2 cells	107
SEHPA	Polyamidoamine-aptamer-coated HMSN for the co-delivery of sorafenib and CRISPR/Cas9	Passively targeting and EPR effects	Sorafenib	Liver cancer	Good stability, enabled ultrahigh drug loading, targeted delivery, and controlled-release of the gene-drug combination	Subcutaneous and orthotopic HCC tumors and HepG2 cells	108
Janus	Janus-structured gold triangle-MSNs	FA targeting	Tirapazamine	Liver cancer	Radiosensitive, photothermal antitumor effects, remarkable tumor growth inhibition without systematic toxicity	Subcutaneous and orthotopic HCC tumors and HepG2 cells	109
FA-JGMSNs	Ber into FA targeting Janus gold MSNs	FA targeting	Berberine	Liver cancer	Highly efficient anti-tumor effect, good biosafety, and radiosensitizers for expanding radiotherapeutic effects	Subcutaneous and orthotopic HCC tumors and SMMC-7721 cells	110
SO-Au-MSNs	Au nanoshell, MSNs and sorafenib	Passively targeting and EPR effects	Sorafenib	Liver cancer	High cell inhibition rate, enhanced toxicity of SO under hyperthermia, and synergistic chemo/photothermal therapy	Huh-7, SMMC-7721, and HepG2 cells	111
PAC-HMHA	Hyaluronic acid, HMSN	Passively targeting and EPR effects	Paclitaxel	Liver cancer	Enhanced tumor inhibition rate	Subcutaneous and orthotopic HCC tumors and SMMC-7721 cells	112

(*continued on next page*)

Table 1 (*continued*)

Nanodrug name	Component	Targeting	Loading agent	Liver disease	Characteristic	Experimental model	Ref.
M-LPMSN-NiAsO x-FA	Magnetic large-pore MSN, ATO prodrugs, large-pore MSNs	Passively targeting and EPR effects	Arsenic trioxide	Liver cancer	Enhanced tumor inhibition and real-time tumor monitoring	Subcutaneous and orthotopic HCC tumors and HepG2 cells	113
MMSNs@SO	Manganese doped MSNs and sorafenib	Passively targeting and EPR effects	Sorafenib	Liver cancer	On-demand drug release in the TME and inducing the ferroptosis of HCC cells	Subcutaneous and orthotopic HCC tumors and HepG2 cells	114
MSN-LA	MSNs, sorafenib, VEGF targeted siRNA, and lactobionic acid	ASGPR-targeting	Sorafenib and siVEGF	Liver cancer	Inducing S cell cycle arrest, enhances the cytotoxicity and improves the tumor target of SO and siVEGF, but also enhances the siVEGF transfection efficiency	Subcutaneous and orthotopic HCC tumors and HepG2, Huh7 cells	115
Janus nanoplatform	Silver/silica MSNs and indocyanine green	FA targeting	Indocyanine green	Liver cancer	Synergistic therapeutic capabilities both *in vitro* and *in vivo*	Subcutaneous and orthotopic HCC tumors and HepG2 cells	116
MSN-GA-CUR	Curcumin, glycyrrhetinic acid, and MSNs	Glycyrrhetinic acid targeting	Curcumin	Liver cancer	Enhanced cytotoxicity and cellular uptake	Subcutaneous and orthotopic HCC tumors and HepG2 cells	117
UA@MSN-UA	Manganese doped MSNs and ursolic acid	Passively targeting and EPR effects	Ursolic acid	Liver cancer	Higher proliferation inhibition, cell cycle arrest at the G2/M phase	HepG2 cells	118
Berberine-loaded Fe_3O_4-mSiO_2 NPs	Janus magnetic MSNs, Fe_3O_4 head, MSNs, and berberine	Fe_3O_4 targeting	Berberine	Liver cancer	High specificity and higher endocytosis capacity	HepG2 cells	119
LHD/miR-375	HMSN, DOX hydrochloride, and miR-375	Passively targeting and EPR effects	DOX hydrochloride and miR-375	Liver cancer	Synergistic antitumor effect by promoting apoptosis	Subcutaneous and orthotopic HCC tumors and HepG2 cells	120
MSN-CS-LA	MSNs, sorafenib, ursolic acid, and lactobionic acid	ASGPR-targeting	Ursolic acid	Liver cancer	Enhanced bioavailability of hydrophobic drugs, efficient tumor cell targeting, and exhibited pH-responsive function and sustained release profile	SMMC-7721 cell and H22 tumor-bearing mice	121
SAB@MSNs-RhB	The rhodamine B covalently grafted SBA-15-structured MSNs and salvianolic acid B	Passively targeting and EPR effects	Salvianolic acid B	Hepatic fibrosis	Enhanced cellular drug uptake, the drug bioaccessibility, and efficacy for anti-ROS/hepatic fibrosis	LX-2 cells	122

NPs, nanoparticles; Gal, galactosamine; PDA, polydopamine; MSNs, mesoporous silica nanoparticles; Asp, aspirin; siPCSK9, small interfering RNA targeting proprotein convertase subtilisin/kexin type 9; EPR, enhanced permeability and retention; MF, manganese-doped mesoporous silica nanoparticles; SOR, sorafenib; PEG, polyethylene glycol; ATO, arsenic trioxide; HMSN, hollow mesoporous silica nanoparticles; DOX, doxorubicin; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; COSM, chitosan-oleic acid-mesoporous silica nanoparticles; APAP, acetaminophen; ISO, isohamnetin; PD-L1, programmed death-ligand 1; NOSH-aspirin, nitric oxide and hydrogen sulfide-releasing aspirin; LNP, lipid nanoparticle; PM, platelet membrane; ERK/mTOR, extracellular signal-regulated kinase/mammalian target of rapamycin; CPPO, bis(2,4,6-trichlorophenyl) oxalate; Ce6, chlorin e6; mSCCC, hybrid nanoparticles composed of mesoporous silica, calcium peroxide, and chemiluminescent agent for PDT therapy; TLS11a, thioaptamer liver cancer-specific sequence 11a; TAT, *trans*-activator of transcription; FFA, free fatty acids; FA, folic acid; DM-NCTD, dimethyl-norcantharidin; PEO-PPO-PEO, poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide); CPT-11, irinotecan; Ber, berberine; siVEGF, small interfering RNA targeting vascular endothelial growth factor; ASGPR, asialoglycoprotein receptor; miR, microRNA; HCC, hepatocellular carcinoma.

inflammatory responses at high concentrations, while positively charged MSNs, although more readily taken up by cells, may disrupt cellular membranes and induce cytotoxicity[125]. Surface modifications, such as PEGylation, enhance biocompatibility by extending circulation time and reducing recognition by the RES. Long-term studies on the biodistribution and clearance of MSNs are crucial for understanding their potential chronic toxicity, as MSNs primarily accumulate in the liver, spleen, and kidneys, where they are gradually degraded and excreted.

The immune response to MSNs is another important consideration, as unmodified MSNs may activate the complement system and induce the production of pro-inflammatory cytokines, and surface coatings with anti-inflammatory agents or immunomodulatory compounds can mitigate these effects, thereby improving compatibility with the immune system[126]. For intravenous applications, hemocompatibility is vital since unmodified MSNs may induce hemolysis, platelet aggregation, and coagulation. Hydrophilic polymer coatings, such as PEG or chitosan, can improve hemocompatibility and reduce thrombotic risks[127,128]. The potential genotoxic and carcinogenic effects of MSNs are under investigation, with current evidence suggesting minimal genotoxicity at therapeutic concentrations, though high doses or prolonged exposure may potentially cause DNA damage and genomic instability. Zhang et al.[129] found that MSNs at a concentration of 120 μg/mL did not cause chromosomal alterations or gene mutations in EGFR or KRAS genes but significantly altered the expression of many genes in human embryonic kidney 293 cells. In summary, while MSNs exhibit a favorable safety profile, their potential toxic effects depend on their physicochemical properties and surface modifications. Thus, it is essential to optimize MSN design to enhance biocompatibility and ensure safe clinical use, particularly in liver physiology and pathology.

5. MSN for the manipulation of liver tumor

In light of the liver's intricate structure, multiple functions, and diverse cell types, a focus on the physiological and pathological environments of the liver is essential in the design of Nano-DDS. In this review, we talk about the design of MSNs-based Nano-DDS on the manipulation of the liver in pathological states, which are broadly classified into tumor states and inflammatory states (Fig. 4). Tumor states encompass a wide range of conditions, from benign growths to malignant cancers, from primary liver cancer to secondary liver cancer, and from hepatocellular carcinoma to cholangiocarcinoma and mixed cell carcinoma, each presenting unique challenges in diagnosis and treatment[130]. In the realm of inflammatory states, our focus primarily lies on liver hepatitis, cirrhosis, and ischemia-reperfusion injury (IRI). Liver fibrosis, which is often a consequence of persistent hepatitis, leads to the formation of scar tissue[131], while IRI results from temporary loss and subsequent restoration of blood supply during liver operations, causing severe tissue damage[132].

5.1. Tumor microenvironment and liver cancer progression

5.1.1. Tumor state

The state of liver tumors is a multifaceted issue, encompassing the complex interplay between the tumor microenvironment (TME) and epidemiological factors[133]. TME is a complex and dynamic network that includes various cell types, such as cancer cells, immune cells, fibroblasts, endothelial cells, and a multitude of signaling molecules that collectively facilitate tumor progression and metastasis[134]. Among them, cancer-associated fibroblasts (CAFs) secret growth factors and cytokines, which not only stimulate the formation of new blood vessels, providing nutrients and oxygen to the tumor but also enhance the tumor cells' ability to invade. The high metabolic activity of tumor cells is redirected to glycolysis and results in the production of lactic acid, creating acidic TME with a low pH environment that promotes cancer cell survival and invasion and therapy resistance[135]. Reactive oxygen species (ROS) are byproducts of cellular metabolism and are further elevated in cancer cells due to a high metabolic rate and mitochondrial dysfunction, which is often accompanied by oxidative stress, as an imbalance between the production of and the body's antioxidant defenses. Simultaneously, cancer cells often upregulate antioxidant systems, such as glutathione (GSH), to counteract ROS-induced damage and maintain a conducive environment for their growth and survival. The concentration of GSH within tumor cells (2−10 mmol/L) is approximately 1000 times higher than the extracellular GSH concentration (2−20 μmol/L) and several times higher than that in normal cells. In turn, this elevated level of GSH often results in an enhanced antioxidative stress capacity in tumor cells, which is accompanied by a significant increase in drug resistance[136]. Enzymatic activity within the TME, such as matrix metalloproteinases (MMPs), which degrade the ECM, is also significantly altered, thereby enabling cancer cells to invade neighboring tissues and metastasize[137]. Furthermore, the interaction between tumor cells and immune cells creates an immunosuppressive environment; tumor cells secrete immunosuppressive cytokines and recruit regulatory T cells and myeloid-derived suppressor cells (MDSCs), which inhibit the activity of cytotoxic T cells and natural killer cells, allowing the tumor to evade the immune system[138]. These characteristics of TME, including low pH, oxidative stress, high GSH, enhanced enzymatic activity, and immune suppression, interplay to create a supportive niche for tumor growth and spread.

5.2. MSN based anti-tumor Nano-DDS

5.2.1. pH-responsiveness

Lower pH is identified as one of the major features of TME[139]. The average pH is 7.4 in the normal tissue, while it is typically measured at 6.5−7.2 in tumors and even lower to 4.5−5.5 in the organelles, such as late endosomes and lysosomes. Researchers have reported various strategies for designing the most efficient pH-sensitive MSNs based on Nano-DDS. One of the principal, widely examined methods is the introduction of a pH-responsive linker for binding a pore capping agent[140]. For example, an acid-responsive acetal linker was widely utilized for the loading and release of drugs from MSNs[141]. Another possibility is to use a hydrazone bond, as in the case of the photosensitizer zinc (II) phthalocyanine (ZnPc) bound to stellate mesoporous silica (SMSN) to achieve controlled and enhanced PDT of cancer (Fig. 5A)[142]. The conjugation of ZnPc onto SMSN resulted in quenching the fluorescence emission and inhibiting ROS generation, whereas photodynamic properties were established again once the photosensitizer was released. pH-responsive shells for MSNs have also been explored. MSNs loaded with DOX and coated with a polymer shell sensitive to H_2O_2 and pH changes were shown to be effective in targeted drug delivery *via* CD44 receptor-mediated endocytosis, where H_2O_2 and pH changes trigger the release of DOX in the tumor microenvironment[143]. In another strategy, MSNs loaded with DOX were coated with a

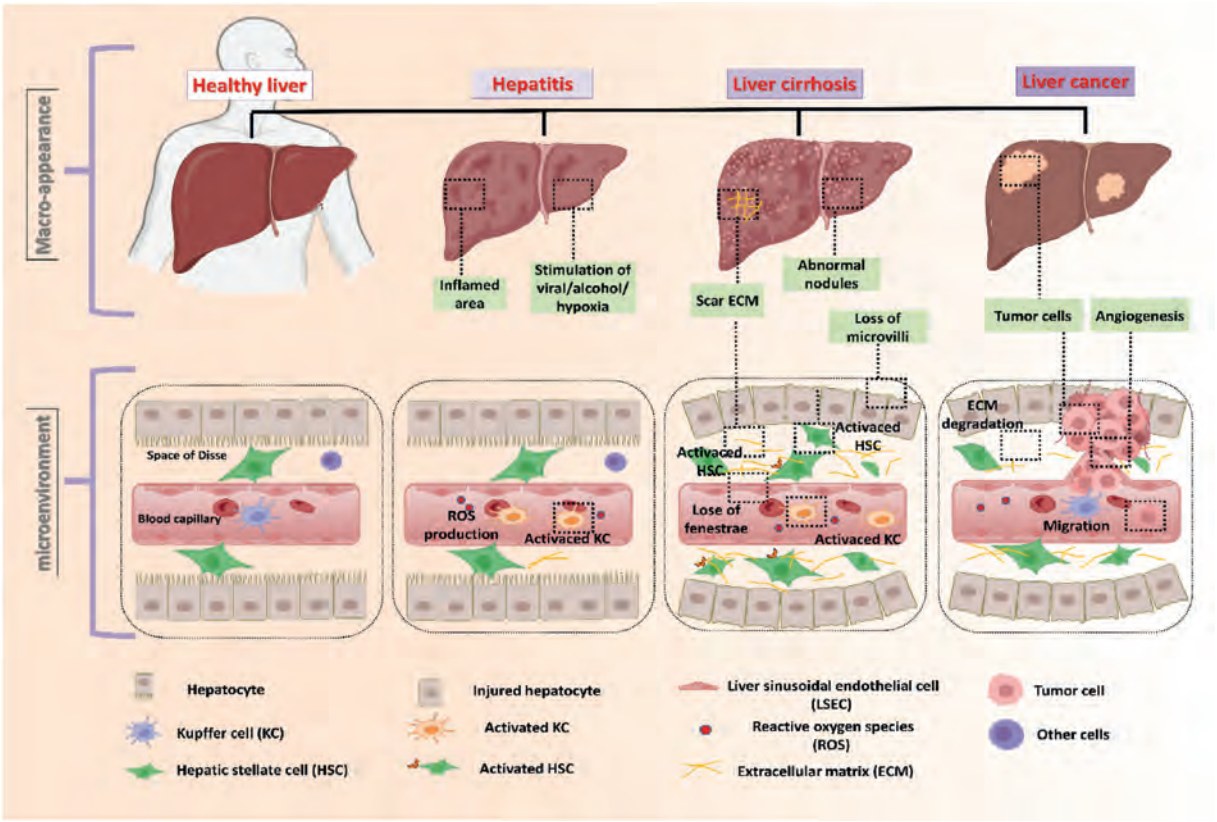

Figure 4 Pathological changes and microenvironment of hepatic diseases.

polymer shell composed of tannic acid/tetraethylenepentamine (TA/TEPA), which could reversibly swell upon pH changes, enabling enhanced DOX release at pH 6.8 and 5 compared to physiological pH. This Nano-DDS was also functionalized with HER-2 antibody as a targeting ligand, which facilitated NP accumulation in cancer tissues and effectively inhibited tumor growth through targeted DOX delivery (Fig. 5B and C)[107]. Wu et al.[144] proposed an effective pH and redox-triggered controlled release system, in which the two amide bonds of ZnO quantum dots coupled by disulfides were attached to the outer surface of HMSN in the form of covalent bonds, and then DOX was encapsulated in the cavities and pores of HMSN to minimize the early release of the drug (Fig. 5D)[144]. Similarly, a redox-responsive system utilizing disulfide-linked ZnO quantum dots attached to hollow MSNs was developed for trigger-controlled DOX release in the presence of tumor-specific reducing agents[145].

5.2.2. *Enzyme-responsiveness*

In tumors, enzymes such as MMPs, hyaluronidase (HAase), and lysosomal cysteine protease cathepsin B are often overexpressed. Researchers have investigated the enzyme-responsiveness of MSNs-based Nano-DDS to stimulate therapeutic activity at the tumor site[146]. For example, organotin-based metallodrug was covalently attached to the MSN surface through a GFLG tetrapeptide linker, which was highly sensitive to the lysosomal cysteine protease cathepsin B that is overexpressed in breast adenocarcinoma. Both *in vitro* and *in vivo* studies demonstrated preferential antitumor ability. Alternatively, Vaghasiya et al.[147] incorporated collagen coating to control the release of Cisplatin (Cis) from MSNs in response to overexpressed MMP-2 (Fig. 6A)[147]. A 2.4-fold higher amount of Cis was released when MMP-2 was present, implying good responsiveness and efficient capping capacity of the designed system. Besides, MSNs were functionalized with triphenylphosphine (TPP), a mitochondria-targeting compound, and encapsulated with DOX by the addition of HA. This design endowed MSNs with pore sealing and targeting capability, as well as sensitivity to cancer-overexpressed HAase[148]. Dual enzyme-responsive DDS was also reported, such as in the case of fluorescence-doped MSNs (FMSN), shelled with HA and collagen I, which are degraded by MMP-2 and HAase in tumor cells to release DOX[149]. When considering the Nano-DDS constructed for simultaneous therapy and imaging, a recent study reported MMP-2-responsive drug delivery based on the core/shell Fe_3O_4@MSN Nano-DDS modified with a peptide PLGVR substrate[150]. In addition to the enzyme-responsive DOX delivery upon reaching the cancer tissue, magnet-guided composite accumulation in the tumors was demonstrated *in vivo*, while the presence of Fe_3O_4 allowed enhanced capabilities for T2-weighted magnetic resonance imaging (MRI) of cancer.

5.2.3. *Redox responsiveness*

TME is characterized by a significant redox imbalance, primarily due to elevated levels of ROS and altered concentrations of reducing agents like GSH. This oxidative stress is a hallmark of cancer and plays a crucial role in tumor progression, metastasis, and drug resistance. Sedighi et al.[151] reported amino-functioned MSNs coated with cerium oxide NPs (CNPs) *via* covalent conjugation for the controlled delivery and release of tyrosine kinase inhibitors (TKIs). Under physiological conditions, CNP-

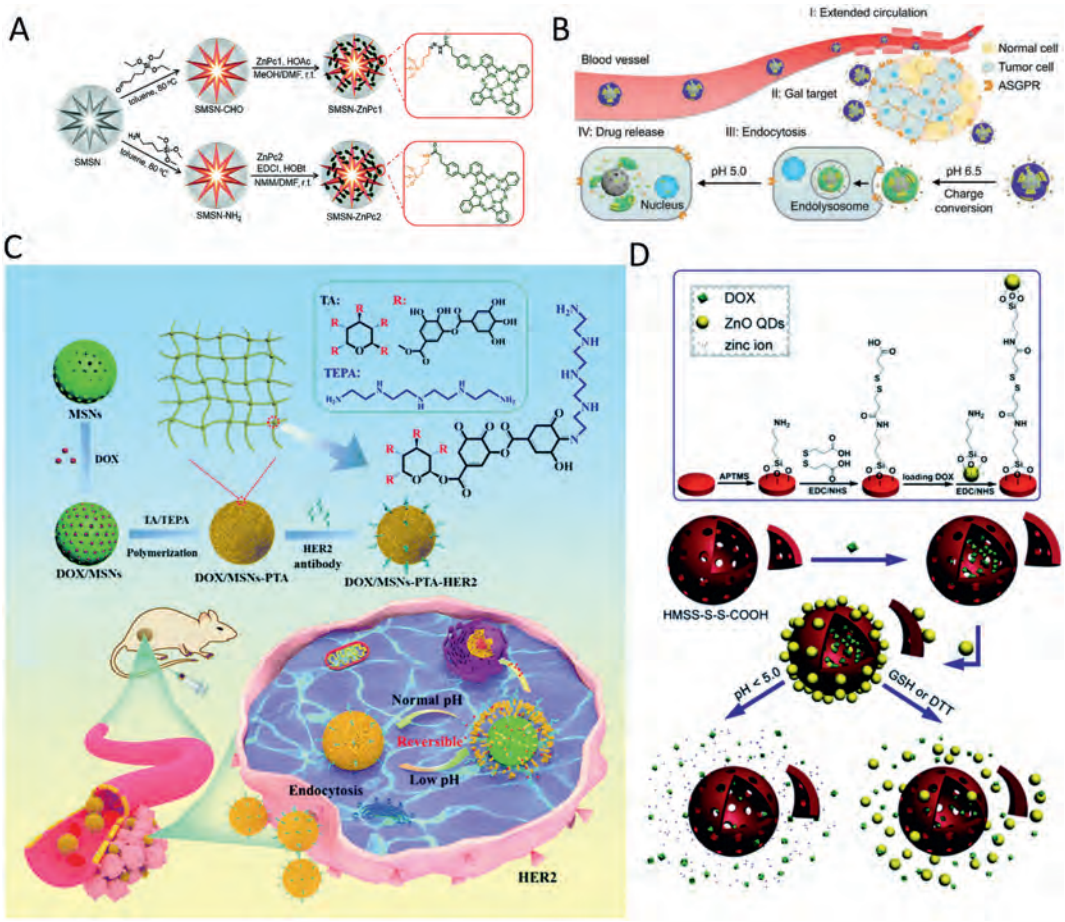

Figure 5 pH-responsive MSNs for enhanced cancer therapy. (A) Preparation of cleavable SMSN−ZnPc1 and non-cleavable SMSN−ZnPc2; reprinted with the permission from Ref. 142. Copyright © 2013 Royal Society of Chemistry. (B) Stepwise targeting and responsiveness of the lipid-coated NPs GPDC-MSNs; Reprinted with the permission from Ref. 108. Copyright © 2020 Ivyspring International Publisher. (C) Schematic illustration of synthesis of DOX/MSNs-PTA-HER2 and drug delivery process of DOX/MSNs-PTA-HER2 in the acidic tumor microenvironment; Reprinted with the permission from Ref. 108. Copyright © 2020 Ivyspring International Publisher. (D) Controlled release of DOX from aZnO-gated HMSS delivery system in response to acidic pH conditions and disulfide reducing reagents (GSH or dithiothreitol); Reprinted with the permission from Ref. 144. Copyright © 2015 Royal Society of Chemistry.

capped MSNs demonstrated a sustained drug release over time as a result of CNPs' gatekeeping effect on the payloads[152]. After the uptake by cancer cells, CNPs created ROS to induce apoptosis. The functionality of CNPs is strongly dependent on the dual oxidation state and the pH of cell compartments[153]. In addition, multifunctional pH/H_2O_2 dual-responsive chiral rod-shaped MSNs (HA-CD/DOX-PCMSRs) were constructed by first grafting phenylboronic acid pinacol ester (PBAP) onto the amino-functioned MSNs, then incorporating DOX into the nanopores, and finally coating with the cyclodextrin-modified HA conjugate (HA-CD) through a weak host−guest interaction. In TME, the pH-responsive and H_2O_2-sensitive moieties of CD and PBAP were exposed, and DOX was leaked for cancer therapy[143].

Besides, higher levels of GSH in cancer cells are critical for detoxifying ROS and preventing oxidative stress. A common approach is to utilize disulfide bonds, which are stable under normal physiological conditions but are cleaved inside the tumor cells at higher levels of GSH, thus releasing the encapsulated drugs exactly where it is needed. For example, Li et al.[145] reported a supramolecular MSNs-based Nano-DDS, which was dual functionalized by aggregation-induced luminescence tetraphenylethylene molecules and supramolecular switches of tilt aromatic hydrocarbons with the assistance of disulfide bonds. This Nano-DDS not only kills tumor cells by releasing drugs under acidic conditions and high concentrations of GSH but also effectively indicates tumor sites by its own fluorescence enhancement under GSH stimulation. Huang et al.[154] directly incorporated disulfide bonds into the silica skeleton of HMSN with high dispersion and particle size below 50 nm, which can break down upon contact with the TME for the rapid release of tumor-reactive drugs. The ultra-small particle size of HMSN guaranteed their high accumulation in tumor tissue, leading to high chemotherapy outcomes. Moreover, diselenide-bridged MSNs provide an additional layer of dual responsiveness in cancer-cell-mimetic protein delivery (Fig. 6C)[155]. These NPs degraded under oxidative and redox conditions found in the TME, ensuring precise drug delivery to the cancer cells. The long circulation time enabled by cloaking MSNs with cancer cell membranes further enhances targeting and therapeutic efficiency. Recent advancements in shape-engineered MSNs, such as virus-like and sphere-like mesoporous theranostic hollow manganese silica (MTHMS) particles, have opened new avenues for cancer

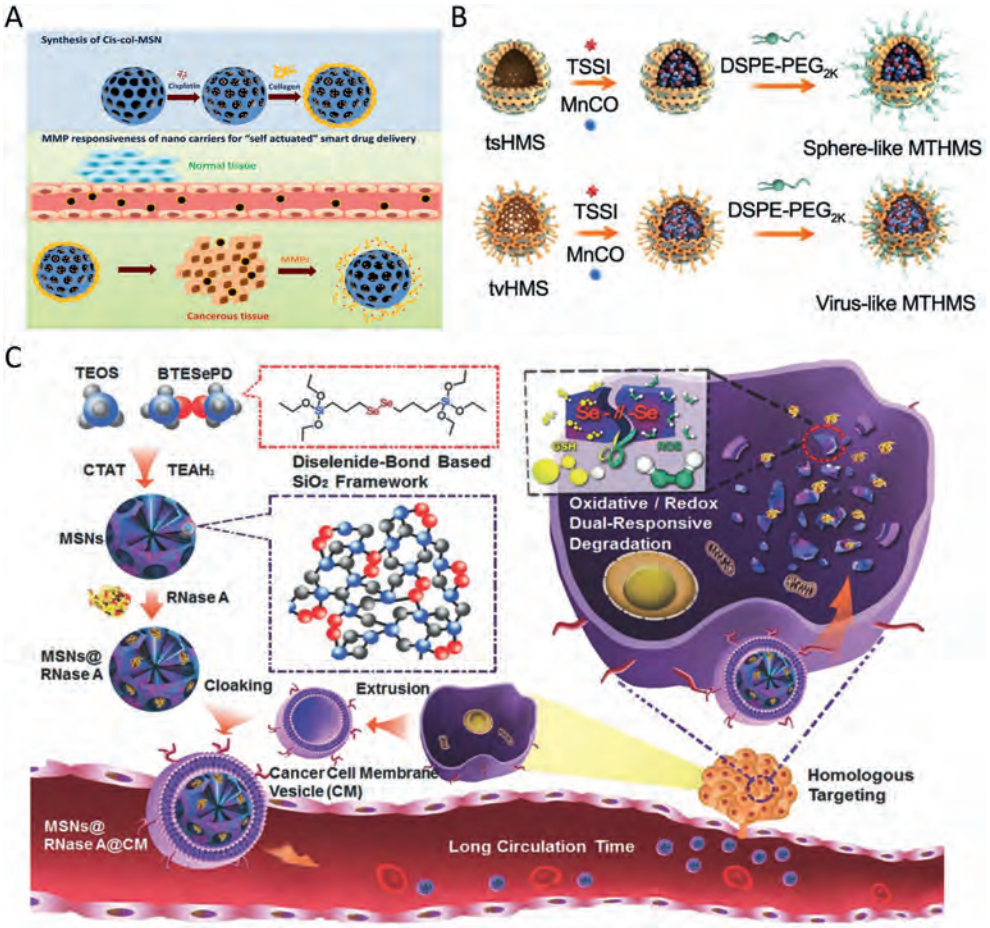

Figure 6 Enzyme-responsive and ROS-responsive MSNs for enhanced cancer therapy. (A) Matrix metalloproteinase-responsive MSNs cloaked with cleavable protein for cancer therapy; reprinted with the permission from Ref. 147. Copyright © 2020 American Chemical Society. (B) Schematic diagram of fabrication of virus-like and sphere-like MTHMS (scale bar = 50 nm); Reprinted with the permission from Ref. 156. Copyright © 2023 The Author(s). (C) Schematic illustration of the synthesis procedure of biodegradable diselenide-bridged MSNs and applications for dual-responsive, cancer-cell-membrane-mimetic protein delivery; Reprinted with the permission from Ref. 155. Copyright © 2018 WILEY-VCH Verlag GmbH & Co., KGaA, Weinheim.

therapy (Fig. 6B)[156]. In this case, GSH-triggered degradation of the hybrid HMONs ensured the direct release of therapeutic agents at tumor sites, making GSH a target for designing antitumor Nano-DDS[157]. These uniquely shaped NPs, engineered with Trithienylsilyl (TSSI), Manganese Carbonyl (MnCO), and PEG coatings, offered superior drug loading and release characteristics, mimicking biological structures for enhanced tumor targeting.

5.2.4. Active targeting

To our knowledge, passive targeting of liver tumors can be rationalized as the accumulation of NPs within cancer tissues by means of the EPR effect. This process not only targets cancer cells but also interferes with multiple drug resistance (MDR) mechanisms by regulating the expression of apoptosis-related genes and inhibiting DNA repair processes, ultimately overcoming MDR in cancer therapy (Fig. 7A)[158]. By comparison, active targeting involves modifications on the surface of NPs with ligands for specific interaction with overexpressed receptors. Targeting ligands such as FA and HA have been widely utilized. Cheng et al.[159] used FA conjugated to PDA-modified MSNs (MSNs@PDA-PEG-FA) to target folate receptors on cancer cells for targeted cancer therapy. In contrast, HA targets the CD44 receptor, a cell surface glycoprotein that is overexpressed in many tumors. MSNs coated with HA selectively accumulate in CD44-positive cancer cells, thereby facilitating the efficient delivery of therapeutic agents. For example, Zhao et al.[160] developed a redox and enzyme-dual stimulus-responsive Nano-DDS (MSN-SS-HA) based on MSNs, where HA was conjugated to the silica surface *via* cleavable disulfide bonds. *In vitro,* drug release profiles showed that the release of DOX was limited under neutral and slightly acidic conditions but was significantly accelerated by the addition of GSH and HAase. In human HCT-116 cells (CD44 receptor overexpression), enhanced cellular uptake *via* CD44 receptor-mediated endocytosis was observed, resulting in higher cytotoxicity to these cells than to non-targeted cells. In addition, peptides such as the RGD (arginine-glycine-aspartate) sequence, which targets integrins overexpressed on tumor endothelial cells and certain cancer cells, have been used to enhance the delivery of drugs to the tumor vasculature and tumor cells[161], and antibodies and antibody fragments (*e.g.*, trastuzumab, which targets the HER2 receptor in cancer) have been used to improve specificity and efficacy. Zhang et al.[162] reported a novel MSNs-based Nano-DDS for triplex cancer therapy *in vitro* and *in vivo* (Fig. 7C)[162]. The mesopores of MSNs containing DOX were capped by cytochrome *c* (CytC) *via* a

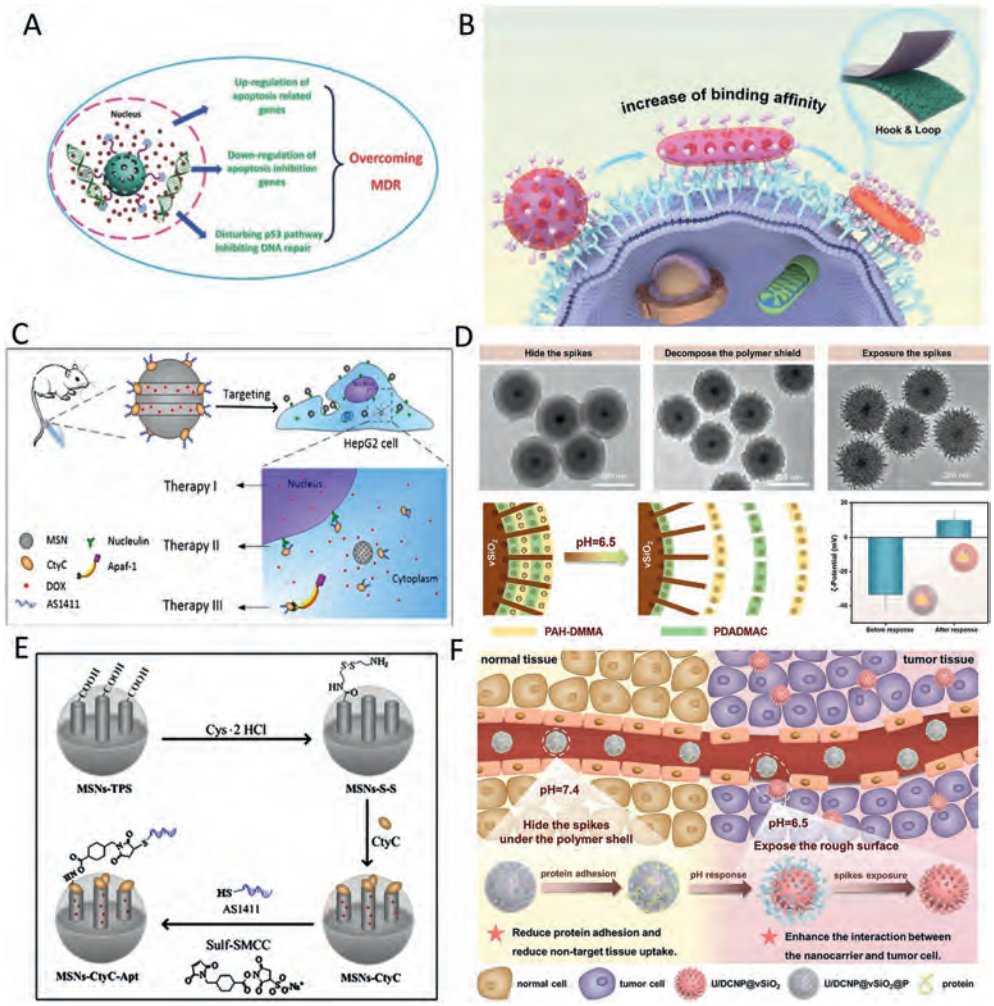

Figure 7 Active targeting MSNs for enhanced cancer therapy. (A) Nuclear-targeting MSNs for overcoming multidrug resistance of cancer cells; reprinted with the permission from Ref. 158. Copyright © 2015 Wiley-VCH. (B) "Hook & Loop" multivalent interactions based on disk-shaped NPs strengthen active targeting. Reprinted with the permission from Ref. 164. Copyright © 2023 Elsevier B.V. All rights reserved. (C) Schematic illustration of triplex cancer therapy based on MSNs for tumor cell-specific endocytosis and intracellular redox-responsive drug delivery; Reprinted with the permission from Ref. 162. Copyright © 2014 Elsevier. (D) Schematic illustration of tumor microenvironment triggered surface roughness transformable nanocarrier for efficient drug delivery. Reprinted with the permission from Ref. 163. Copyright © 2023 Wiley-VCH GmbH. (E) Synthetic route of MSNs−CytC−Apt; Reprinted with the permission from Ref. 162. Copyright © 2014 Elsevier. (F) Camouflaged virus-like-nanocarrier with a transformable rough surface for boosting drug delivery. Reprinted with the permission from Ref. 163. Copyright © 2023 Wiley-VCH GmbH.

linker of redox-cleavable disulfide bonds to MSNs. A G-rich oligonucleotide DNA aptamer AS1411 was employed as a specific targeting motif to ensure selective delivery to cancer cells. Once endocytosing by the tumor cells, GSH would lead to the breakage of disulfide bonds for the delivery of DOX. The detached AS1411 molecules would bind with nucleolin in the nuclear membrane and block some functions of nucleolin to cause DNA damage. The detached CytC would combine with the apoptotic protease activating factor (Apaf-1), in turn activating the caspase cascade, leading to cell apoptosis (Fig. 7E)[162]. Another application explored the differential response of NPs in normal *versus* tumor tissues (Fig. 7F)[163].

Besides ligand modifications, clever applications of NP morphology and topology can also significantly enhance tissue penetration and active targeting efficiency. For instance, one innovative strategy involved designing NPs with a "Hook & Loop" mechanism, which increased their binding affinity to cancer cells through specific surface interactions (Fig. 7B)[164]. This approach allowed the NPs to effectively retain at the tumor site, enhancing their interaction with the TME and improving drug delivery efficiency. Another unique application of NP surface modifications was the use of pH-responsive spikes (Fig. 7D)[163]. This structural transformation allowed NPs to interact with the tumor tissues and deliver drugs in response to the acidic TME. At a normal tissue pH of 7.4, the NPs kept their surface spikes hidden under a polymer shield, reducing unwanted adhesion to healthy cells. However, upon reaching the tumor's acidic environment (pH 6.5), the polymer shield decomposed, exposing the rough surface and promoting greater interaction with tumor cells. This pH-dependent mechanism enhanced the specific targeting of cancerous tissues while minimizing off-target effects.

6. MSN for the manipulation of liver non-tumor diseases

6.1. Liver cirrhosis

6.1.1. Inflammation state

Irritants, including HBV, HCV, drugs, poisonous substances, and alcohol, cause chronic inflammation and liver damage by infecting hepatocytes and evading the host immune response, leading to liver inflammation state and liver injury[165]. When the body is invaded by exogenous pathogens and other agents, the host immune system is activated, and polymorphonuclear neutrophils (PMNs) accumulate to clear pathogens after crossing the vascular barrier; these cells are regulated by apoptosis to maintain constant numbers and homeostasis. Macrophages are key components of the innate immune system. Activated macrophages can generally be divided into two main subtypes: classically activated macrophages (M1), which drive pro-inflammatory responses, and alternatively activated macrophages (M2), which exert anti-inflammatory functions. In the inflammatory microenvironment, activated M1 macrophages induce inflammation and ultimately cause tissue damage by releasing inflammatory mediators such as IL-6, IL-1β, TNF-α, and ROS[166,167]. The level of oxidative stress is positively correlated with the severity of inflammatory diseases[167]. The body's immune response to these infections also includes the activation of immune cells such as T lymphocytes and the activation of HSC, which contribute to liver injury and the development of cirrhosis.

6.1.2. MSNs for the treatment of hepatitis

MSNs can be designed as a controllable Nano-DDS for inflammation therapy. When they reach the inflammatory site, they can effectively release the drug and apply treatment, wherein the release rate can be regulated by particle pore size, surface functionalization, and the interaction between drugs and mesopores so as to improve the therapeutic effect and reduce system side effects[168]. Kwon et al.[169] used ethyl acetate as a pore-expanding agent to synthesize MSNs with extra-large nanopores (XL-MSNs) for the loading of anti-inflammatory cytokine IL-4. XL-MSNs with a pore size of 30 nm showed significantly higher IL-4 loading amount than that of conventional MSNs with small nanopores, effectively polarized macrophages into anti-inflammatory M2 macrophages in a mouse model. What's more, an MSN-based Nano-DDS was applied for the precise delivery of shDNA molecules targeting the conserved 5'-untranslated region (UTR) of HCV RNA to impede its replication. The functionalization of MSNs with amine and galactose enabled specific targeting of hepatocytes, suggesting their potential as an effective delivery vector for siDNA in the treatment of HCV infection[170]. Mehmood et al.[171] innovated amino-decorated MSNs for the targeted delivery of sofosbuvir in the treatment of HCV, resulting in Fickian diffusion-controlled release of the drug in rats. Additionally, the application of MSNs shows promise in addressing constraints associated with traditional Chinese medicine. Zhang et al.[94] illustrated the protective efficacy of puerarin-loaded MSNs in mitigating alcoholic hepatitis by activating the mTOR-mediated autophagy pathway, thereby reducing the accumulation of fatty droplets in the injured liver.

6.1.3. MSNs for the treatment of liver injury and liver failure

Once overwhelming hepatocyte necrosis, the liver function deteriorates, and liver failure occurs with fatal clinical multiorgan dysfunction. Cai et al.[90] developed a novel oral administration strategy using HMSN for the loading of the antioxidant drug astaxanthin to improve their water solubility and liver targeted efficiency. Owing to the ability of HMSN to overcome the physiological barriers in the gastrointestinal tract as well as passively target the liver, it significantly improved the therapeutic effect of astaxanthin on liver injury induced by acetaminophen. Wang et al.[172] assembled hepatocyte growth factor (HGF), acidic fibroblast growth factor (aFGF), and activin A into PEI-modified MSNs (GF-PEI-MSN) as a Nano-DDS for the delivery of growth factors to treat liver failure. When transplanted into a mice model of CCl_4-induced liver injury, the mouse embryonic stem cells treated with the functionalized Nano-DDS induced more robust differentiation of hepatocyte-like cells and significantly ameliorated liver injury and fibrosis because GF-PEI-MSN promoted a direct differentiation of stem cells toward hepatocyte-like cells.

6.2. Liver cirrhosis

6.2.1. Mechanism of cirrhosis

Major causes of liver cirrhosis include virus infection, alcohol-related liver disease, and NAFLD[4,5]. Normal inflammatory responses are beneficial for the healing of liver injuries, but persistent inflammation under chronic stimulation leads to liver fibrosis. The process of liver fibrosis is influenced by inflammatory signals and interactions between hepatocytes, KC, and HSC[173]. In a healthy liver, HSC stores vitamin A and maintains liver architecture, while upon liver injury, these cells become activated and transform into myofibroblast (MF)[174]. During this process, activated HSC migrates to the site of injury, producing an abundance of ECM and inflammatory mediators and forming scar tissue[175]. Studies have shown that apoptotic bodies produced by hepatocyte apoptosis, when engulfed by HSC, activate them and upregulate the expression of pro-collagen α1, TGFβ1, NADPH oxidase, and intracellular levels of ROS[176]; ROS can directly or indirectly activate the Nucleotide-binding oligomerization domain, Leucine-rich Repeat and Pyrin domain containing (NLRP3) inflammasome, promoting the occurrence of inflammatory responses[177].

6.2.2. MSNs for the treatment of cirrhosis

Albarran et al.[178] reported MSNs functionalized with OH groups and loaded with a promising therapeutic drug, IFC-305, for the treatment of liver cirrhosis. The results showed that the drug was stabilized into the silica xerogel since the corresponding molecular vibrations of the functional groups from IFC-305 remained while incorporated in the xerogel structure. For the samples synthesized with low water content, a stronger interaction between the drug and MSN matrix was favored, generating free OH loss on the nanoparticle surface. With high water content, the band intensity of free OH was lower, indicating a better release behavior due to the formation of hydrogen bonds between the xerogel surface and IFC. Besides, Niu et al.[99] utilized MSNs as a Nano-DDS to enhance the dissolution rate of IMB16-4, improve its oral bioavailability, and inhibit liver fibrosis. IMB16-4-MSNs significantly increased the dissolution rate of IMB16-4, reduced cytotoxicity on human HSC LX-2 at high concentrations, and improved oral bioavailability by up to 530% in rats compared to raw IMB16-4. Furthermore, IMB16-4-MSNs demonstrated the ability to suppress hepatic fibrogenesis by downregulating the expression of hepatic fibrogenic markers. He et al.[122] employed a Nano-DDS known as SAB@MSNs-RhB, which involved the application of rhodamine B (RhB) covalently grafted

SBA-15-structured MSNs to deliver the negatively charged drug salvianolic acid B (SAB) for the treatment of hepatic fibrosis. Compared to SAB-loaded MSNs (SAB@MSNs) with a negatively charged surface, SAB@MSNs-RhB demonstrated superior sustained-release properties, higher release rates, and concentrations of SAB over an extended period following the initial release of the drug. Importantly, SAB@MSNs-RhB enhanced the cellular drug uptake, the drug bioaccessibility, and efficacy for hepatic fibrosis by the NPs-mediated endocytosis and the controlled release of the drug.

6.3. Hepatic ischemia-reperfusion injury and liver transplantation

6.3.1. Mechanism of hepatic IRI

Having discussed liver fibrosis and liver failure, liver transplantation is the only curative therapy for terminal liver disease so far. We then focus on the application and prospects of liver IRI, presenting the phenomenon in the sequence of ischemia followed by reperfusion, which occurs during liver transplantation and major hepatic surgeries. In this process, liver cells undergo hypoxic stress and metabolic dysfunction due to a lack of oxygen and nutrients in their microenvironment. This leads to the activation of hypoxia-limiting enzymes such as aldehyde reductase AR[179], causing abnormal intracellular metabolism and even triggering cell death.

In the early stages of reperfusion, the transient portal hypertension and shear forces from hyperdynamic stress directly damage the endothelial cells of intrahepatic vessels, leading to the aggregation of platelets and white blood cells in these narrowed areas and releasing a series of inflammation-related signaling factors[180,181]. These changes reduce hepatic microcirculation, further exacerbating hyperdynamic stress and forming a detrimental positive feedback loop, thereby prolonging the duration of hypoxic damage. When the microcirculation environment slightly recovers, the sudden rise in oxygen levels delivers another blow to liver cells, causing severe oxidative stress and inflammatory reactions. This process leads to significant changes in the intracellular reactive environment, tipping the balance toward cell death. The inflammatory responses of these cells, along with exogenous transplanted organs, will also trigger related immune responses, having distinct short-term and long-term effects on liver cells.

6.3.2. MSN DDS for the treatment of hepatic IRI and liver transplantation

To prevent liver damage caused by IRI, as mentioned above, special interventions at various stages and times are necessary during treatment. Yang et al.[182] prepared a synthetic silane coupling agent of TEOS and RhB, which was used to form MSNS-RhB and loaded SalB to prepare SalB@MSNs-RhB. They identified that the slower release of SalB loaded into MSNs-RhB contributed to the enhanced effective action of SalB in the organism. After treatment with SalB and SalB@MSNs-RhB, the liver tissue showed increased Bcl-2 and decreased caspase-3 and Bax levels, suggesting that SalB@MSNs-RhB inhibited apoptosis by inhibiting caspase-3 and Bax and upregulating Bcl-2 to inhibit apoptosi and significant improved the therapeutic effect of SalB. Furthermore, Wang et al.[183] developed a novel colorimetric and luminescence nanosensor utilizing upconversion NPs (UCNPs) for the quantitative measurement of carbon monoxide (CO) *in vitro* and *ex vivo*. The nanosensor incorporated CO-responsive palladium ion-bounded RhB derivatives (Pd-RBDs) within the MSN shell, with particles situated both inside and outside a cyclodextrin (CD) layer. It was employed to assess the protective effects of anti-hepatic IRI oligopeptides in relation to CO exposure, with elevated CO levels observed in Oct-treated hepatic IRI mouse models. Moreover, Ma et al.[184] showed another approach was demonstrated by using ROS-responsive MSNs (rMSN) for delivering siRNA targeting IRF5 (Fig. 8B)[184]. Recent advancements in biomimetic nanotechnology have highlighted the potential of diatom-inspired materials in medical applications, particularly for liver transplantation and the treatment of hepatic IRI. The exogenous silica skeleton of diatoms provides a blueprint for creating robust and flexible biohybrid systems. Biointegrated silicon-based red blood cells (Si-RBCs), modeled on this architecture, exhibit enhanced mechanical stability while retaining the oxygen-carrying capability of natural erythrocytes. These Si-RBCs also demonstrate superior resistance to mechanical and chemical stress. This dual functionality effectively addresses key challenges, including maintaining tissue oxygenation, mitigating oxidative stress, and reducing inflammation and reperfusion injury during transplantation. By enhancing systemic circulation and enabling targeted oxygen delivery, bio-Si-RBCs represent a novel approach for protecting against ischemic damage and improving graft survival, ultimately contributing to better outcomes for liver transplantation patients (Fig. 8A)[185].

7. Conclusions and perspectives

Collectively, MSNs with a wide range of sizes and shapes, distinct morphological properties, and favorable physicochemical features have demonstrated substantial value in biomedical applications, particularly in targeted drug delivery and therapeutic interventions. By precisely controlling pore size, surface charge, and functionalization, as well as engineering the NPs to adapt to the biological environment, MSNs can effectively manage drug release dynamics and target specificity, addressing pathological states such as liver tumor growth and chronic inflammation. The passive targeting, combined with the biocompatibility and modifiability of MSNs, highlights their potential to revolutionize intrahepatic drug delivery. Pathologically, MSNs have been proven to modulate the TME and inflammatory responses, providing an effective platform for the selective targeting of cancer cells and alleviating liver fibrosis.

Despite the promising therapeutic potential of MSN-based Nano-DDS, their translation from laboratory research to clinical applications faces several critical challenges spanning various stages of development, including unpredictable assembly processes, inefficient drug delivery, low-permeability in multiple barriers *in vivo*, insufficient responsiveness to the pathophysiologic/physiopathologic microenvironments, and unresolved biosafety concerns. A major challenge is the unpredictability of MSN assembly, which relies on non-covalent interactions such as hydrophobic forces, hydrogen bonding, and $\pi-\pi$ stacking to form stable nanostructures. These interactions are highly sensitive to environmental changes, leading to inconsistent NP formation. This variability complicates scaling up production from the laboratory to industrial levels, making it difficult to maintain uniform particle size and consistent drug loading, which are crucial for clinical applications. As a result, large-scale manufacturing remains both technically challenging and costly.

The use of MSNs for multicomponent therapies, where multiple drugs are delivered simultaneously, introduces further

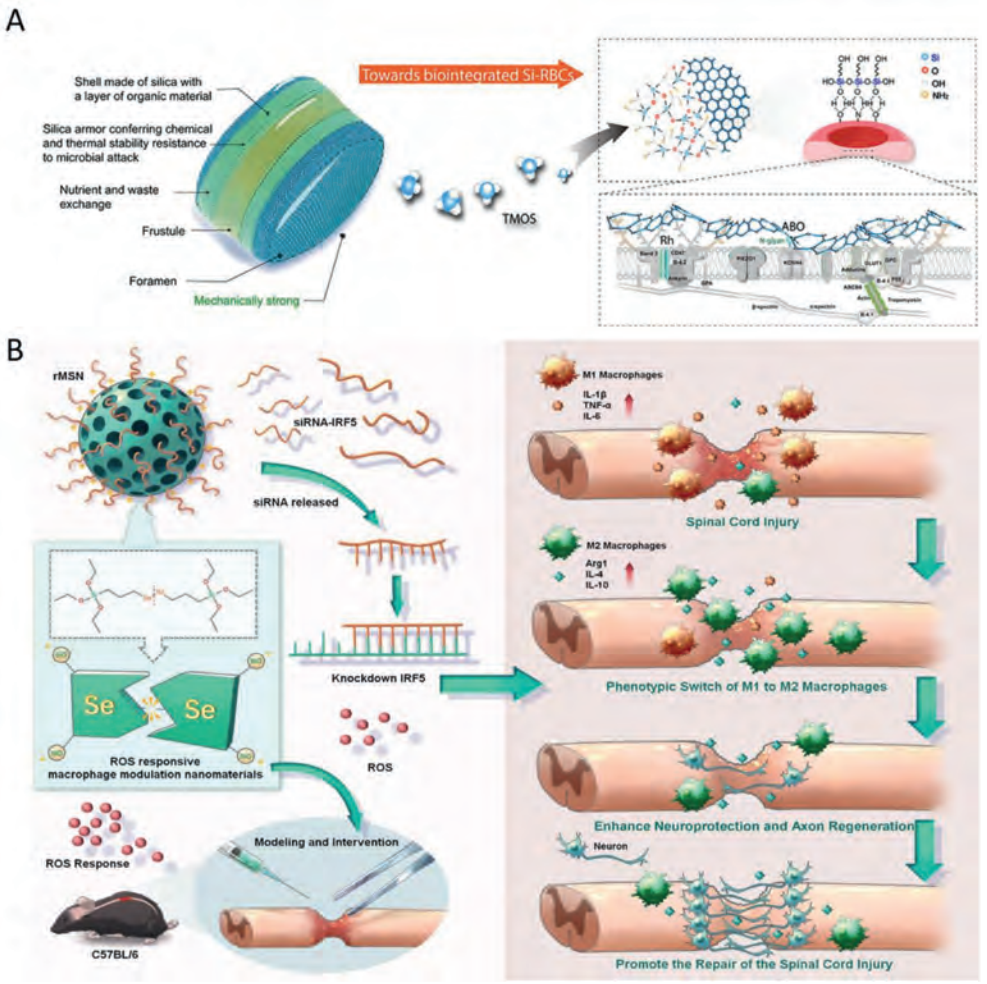

Figure 8 MSNs for the manipulation of liver inflammatory diseases. (A) Schematic representation of biointegrated Si-RBCs derived from biological diatoms, highlighting their robust silica exoskeleton, molecular integration, and functional compatibility for efficient oxygen transport in circulation; Reprinted with the permission from Ref. 185. Copyright © 2024 the Author(s). Published by PNAS. (B)Illustration of the construction of reactive oxygen species responsive mesoporous silica NPs (rMSN) for delivering siRNA-IRF5; Reprinted with the permission from Ref. 184. Copyright © 2022 Wiley-VCH GmbH.

complexities. Optimizing drug ratios, controlling the release of each component, and ensuring synergistic effects between drugs are difficult tasks. From a manufacturing perspective, scaling up production while maintaining batch-to-batch consistency in terms of particle size, drug loading, and therapeutic performance is highly complex and costly. Another key obstacle is the insufficient delivery efficiency of MSNs both *in vitro* and *in vivo*. Once in the bloodstream, MSNs face physical barriers, including mucus, biological films, and solid tissues, and biological barriers, like proteins, immune cells, and enzymes, which all can decrease permeability and cause premature degradation of the Nano-DDS. Moreover, many MSNs lack precise targeting capabilities, resulting in off-target distribution and increasing the risk of systemic toxicity. To overcome this, improvements in delivery efficiency while minimizing off-target effects are essential. Compounding this is the unclear *in vivo* stability and pharmacokinetics of MSNs, as they are often rapidly cleared by the mononuclear phagocyte system (MPS) or filtered out by the kidneys, reducing their therapeutic window. Moreover, the *in vivo* fate of MSNs remains unclear, with unpredictable biodistribution, cellular uptake, metabolism, and excretion. This lack of data on these behaviors within biological systems presents a significant challenge to ensuring both safety and efficacy, making it difficult to gain regulatory approval and advance MSNs through clinical trials. Additionally, small animal models used in testing often fail to accurately mimic human pharmacokinetics, leading to poor clinical trial outcomes.

Biosafety and immunogenicity are also critical concerns. Without protective carriers, MSNs may interact directly with immune cells, potentially triggering immune responses and causing side effects like inflammation. While early studies suggest favorable safety profiles, there is a lack of long-term data regarding their effects on major organs and potential tissue accumulation, raising concerns about long-term toxicity. Future studies will focus on exploring the biosafety of MSNs as Nano-DDS, their toxicity within the human body, and their delivery efficiency *in vivo*, aiming to genuinely improve disease treatment outcomes.

While MSNs offer great promise for drug delivery and disease treatment, several challenges must be addressed to ensure their successful transition from bench to bedside. These include improving assembly predictability, enhancing delivery efficiency,

understanding *in vivo* pharmacokinetics, ensuring safety, and developing scalable manufacturing processes. With a deeper understanding of biomedical nanomaterials and continuous technological advancement, MSNs are expected to play an increasingly vital role in the diagnosis and treatment of liver diseases, thereby significantly enhancing patient quality of life.

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Author contributions

Heran Li and Zhiye Bao designed the research. Xuchun Chen, Bingxin Zhou, Ruilin Zhou and Ze Zhu helped to conceptualization. Boyan Liu, Wenshi Liu and Miao Xu wrote the original draft. Heran Li, Keke Wang, and Tongyi Zhao revised the manuscript. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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