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REVIEW

Nanomedicines in the Treatment of Liver Fibrosis: A Review

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Abstract: Liver fibrosis is a reversible pathological process caused by chronic liver injury, which can lead to severe complications such as liver failure and cirrhosis. Current clinical treatments mainly focus on managing the underlying causes and complications, such as using antiviral regimens for HBV/HCV infections, combining alcohol abstinence with nutritional support for alcoholic fibrosis, and emphasizing weight reduction and exercise in metabolic associated steatolipodystrophy or non-alcoholic steatohepatitis. However, traditional therapies often have limited efficacy and significant side effects. With the deepening understanding of the pathophysiology of liver fibrosis, new therapeutic targets and investigational drugs are being continuously discovered. For example, lanifibranor and efruxifermin have shown promise in clinical trials. Although methods such as FXR and PPAR agonists, fibroblast growth factor 21 analogs, and mesenchymal stem cell therapies hold potential, they are limited by suboptimal delivery to the target site and systemic adverse reactions. Nanomedicine offers a solution by enabling the direct, precise, and efficient delivery of antifibrotic agents to fibrotic sites. This review explores the pathological mechanisms of liver fibrosis, the current state of clinical treatments, and the application of nanomedicine in the diagnosis and treatment of liver fibrosis. It also discusses the challenges in translating nanomedicines from laboratory research to clinical application and suggests potential improvements, aiming to enhance the understanding of liver fibrosis and provide new insights and approaches for its reversal and potential cure.

Keywords: nanomedicine, liver fibrosis, targeted therapy, drug delivery systems, combination therapy

Introduction

Chronic liver disease remains a major global public health concern, accounting for approximately 2 million deaths annually, which represents 4% of total global mortality.[1] Liver fibrosis (LF) refers to the excessive accumulation of connective tissue, such as collagen, in the liver as a result of prolonged injury, leading to structural and functional alterations in the organ. LF is a common pathological process in the progression of various chronic liver diseases and represents the final reversible stage before the onset of cirrhosis. Without timely intervention, LF can progress to cirrhosis and eventually to irreversible hepatocellular carcinoma (HCC). In most cases, LF develops insidiously, with no obvious clinical symptoms in the early stages, and progresses slowly. Therefore, early diagnosis and timely treatment are crucial to inhibiting or reversing LF, delaying the progression to cirrhosis, and preventing liver cancer.[2–4]

Currently, LF diagnosis primarily relies on imaging, serum biomarkers, liver biopsy, and non-invasive techniques.[5] However, imaging methods like ultrasound and MRI elastography have limited sensitivity in early-stage fibrosis, particularly in patients with obesity or fatty liver disease. While serum biomarkers are convenient to assess, their changes may be subtle in the early stages of fibrosis. Moreover, the sensitivity and specificity of these markers can be

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influenced by various factors, including age, diabetes, and the activity of liver inflammation.[6] Liver biopsy, though considered the gold standard, has limitations in diagnosing mild fibrosis due to its reliance on the sampling site, which may not fully represent the pathological state of the entire liver. Consequently, the lack of highly accurate diagnostic tools remains a significant challenge in achieving effective LF treatment.

Moreover, effective therapeutic options for LF remain limited, and the development of antifibrotic drugs continues to face numerous challenges. One major obstacle is the complexity and diversity of therapeutic targets. The development of LF is a multifactorial and multi-pathway process involving immune responses, extracellular matrix (ECM) accumulation, and inflammatory signaling pathways.[7] As a result, targeting a single pathway or molecule for LF treatment is exceedingly difficult. Currently, most antifibrotic drugs focus on intervening in specific pathological processes but fail to comprehensively suppress the formation and progression of fibrosis. Additionally, existing therapeutic agents, including chemical drugs, traditional Chinese medicine extracts, and monoclonal antibodies, are limited by poor water solubility, lack of targeted delivery within the body, and inadequate accumulation in the liver. These factors contribute to low bioavailability and are often associated with significant side effects.[8–10] Therefore, the development of strategies to enhance drug targeting, improve bioavailability, and minimize adverse effects is urgently needed.

With the increasing demand for precision and high-efficiency technologies in the treatment of LF, nanomedicine-based delivery systems are progressively overcoming the limitations of conventional therapies. In targeted delivery, the design of carriers such as nanoparticles and nanocapsules, along with specific surface modifications, enables precise enrichment of drugs in fibrotic areas.[8,9] This targeted delivery not only significantly increases the drug concentration at the lesion site but also reduces the distribution of drugs in non-target organs, thereby enhancing therapeutic efficacy while lowering systemic toxicity risks.

In optimizing drug delivery efficiency, nanomaterials, with their large specific surface area, can not only carry high doses of drugs but also improve the solubility and bioavailability of poorly soluble drugs. Furthermore, through pH-responsive or enzyme-sensitive controlled-release technologies, smart release of drugs can be achieved, avoiding the severe fluctuations in blood drug concentration and the associated side effects that occur with traditional dosing methods.

In terms of expanding therapeutic strategies, nanocarriers offer the possibility of multi-mechanism synergistic intervention. For example, loading anti-fibrotic drugs, antioxidants, and anti-inflammatory drugs into the same carrier can simultaneously inhibit multiple pathogenic pathways,[11] including inflammation activation, oxidative stress, and collagen deposition. When combined with photothermal therapy or photodynamic therapy,[12] local heat generation or reactive oxygen species production can enhance the degradation of fibrous tissue through physical effects. Modulating the behavior of immune cells, such as influencing the polarization phenotype of tumor-associated macrophages (TAMs), enhancing the activity of natural killer (NK) cells, or alleviating T cell exhaustion, also impacts the progression of LF.

Regarding safety, the encapsulation structure of nanosystems effectively isolates free drugs from direct damage to normal tissues. Regulating the sustained release of drugs within the liver can further reduce the risk of drug accumulation in non-target organs. Additionally, nanotechnology can be combined with imaging techniques to dynamically monitor the real-time progression of LF, providing more accurate diagnostic and therapeutic guidance for clinical practice.

This review first explores the pathogenesis of LF, providing a detailed analysis of its pathological processes and the current challenges faced in clinical treatment. It then focuses on the recent advances in the application of nanomedicine-based drug delivery systems for the diagnosis and treatment of LF, covering a variety of therapeutic strategies, including passive targeting, active ligand-targeted delivery, combination therapies, and smart-responsive delivery systems. Finally, the review discusses the challenges and potential improvements associated with the translation of nanomedicine-based drug delivery systems from the laboratory to clinical applications. We hope this review will contribute to a deeper understanding of LF and offer new perspectives and approaches for the reversal and cure of this condition.

Pathological Mechanisms of LF

LF is characterized by abnormal changes in liver structure and function, primarily triggered by prolonged liver injury. The core pathological mechanism underlying LF is the abnormal deposition of extracellular matrix (ECM) components within liver tissue, leading to fibrosis. ECM production is regulated through the coordinated actions of various cell types, including hepatocytes, endothelial cells, and hepatic stellate cells (HSCs). Among these, activated HSCs are the principal

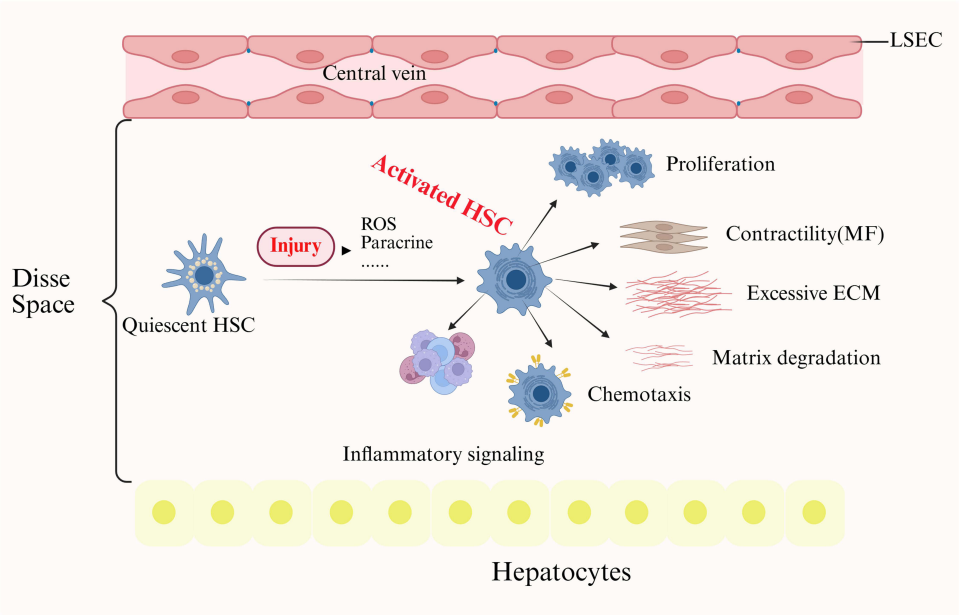

Figure 1 Activation of HSCs. The activation of HSCs, triggered by stimuli such as reactive oxygen species (ROS) and paracrine signals, induces their differentiation into myofibroblasts and transitions into a proliferative, fibrotic state. This process leads to changes in behaviors of HSCs, including proliferation, contraction, fibrosis, matrix degradation, chemotaxis, and inflammatory signaling. LSEC (Liver Sinusoidal Endothelial Cells) are also shown in the figure. Created in BioRender. Niu, R. (2025) https://BioRender.com/0wkjg37.

producers of ECM and play critical roles in the inflammatory response, fibrosis, and angiogenesis in LF (Figure 1). These cells are central to the development of LF and play a pivotal role in driving the fibrotic changes in the liver. Therefore, a series of strategies targeting HSCs can be designed to treat LF.

Characteristics and Functions of Activated HSCs

HSCs are a type of mesenchymal cell located in the space of Disse, between hepatocytes and liver sinusoidal endothelial cells, comprising about 10% of non-parenchymal liver cells. In their quiescent state, HSCs primarily serve as storage cells for vitamin A and retinoids.[7] HSCs are key players in the development of LF and are among the most extensively studied fibro-genic cells.

When the liver is subjected to injury, various liver cells, including hepatocytes, Kupffer cells, liver sinusoidal endothelial cells, macrophages, and platelets, secrete factors such as transforming growth factor (TGF-β), platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF-II), which activate and transdifferentiate HSCs. During activation, HSCs lose their lipid droplets (which contain vitamin A) and differentiate into myofibroblasts (MFs), cells with contraction, migration, and fibrogenic characteristics.[13] Activated HSCs express α-SMA, type I and III collagen fibers (Col I/III, major components of scar tissue), and tissue inhibitors of matrix metalloproteinases, which inhibit the activity of matrix metalloproteinases, disrupting the dynamic balance between ECM deposition and degradation in the liver.[13]

Thus, activated HSCs are crucial targets for LF treatment. Additionally, activated HSCs can secrete fibrogenic cytokines such as TGF-β and PDGF, which further promote HSCs activation through autocrine and paracrine mechanisms. Therefore, blocking the TGF-β or PDGF signaling pathways represents an effective strategy for treating LF.

Malotilate inhibits the activation and proliferation of HSCs by blocking the TGF-β1/Smad signaling pathway.[14] Additionally, multi-targeted tyrosine kinase inhibitors such as imatinib and sorafenib (SOR) act on the PDGF receptor and the Raf/ERK signaling pathway to inhibit the activation of PDGFR, thereby suppressing the activation and proliferation of HSCs.[15] These agents have demonstrated antifibrotic effects in fibrosis animal models. Nilotinib, another tyrosine kinase inhibitor, also inhibits PDGF- and TGF-β-induced ERK and Akt phosphorylation, thereby suppressing HSCs proliferation, migration, and the synthesis of α-SMA and collagen fibers.[16] Moreover, several antifibrotic agents,

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such as the acetyl-CoA carboxylase inhibitor GS-0976, inhibit primary rat HSCs activation by reducing the expression of α-SMA and the production of collagen.[17] Meanwhile, one of the major clinical features of LF is the excessive accumulation of ECM, particularly collagen. Type I collagen is the predominant component of ECM, and its crosslinking is significantly increased in LF. Therefore, reducing Type I collagen has become a therapeutic approach for treating LF. In one study, the monoclonal antibody GS-6624, an inhibitor of the matrix remodeling enzyme LOXL2, exhibited promising therapeutic effects on non-alcoholic steatohepatitis (NASH)-induced liver cirrhosis and fibrosis.[18]

The Relationship Between Inflammation and LF

Moreover, ROS contribute to LF by promoting the activation and proliferation of fibroblasts and myofibroblasts, as well as activating the TGF-β pathway in an autocrine manner. Consequently, inflammation plays a crucial role in the pathogenesis of LF. Anti-inflammatory agents, such as glycyrrhizin derivatives, have been used in the treatment of LF, as they inhibit the activation of HSCs and reduce the progression of LF, providing benefits to patients with alcoholic liver disease and NASH.[19] Another anti-inflammatory strategy involves the use of specific receptor antagonists to neutralize inflammatory cytokines involved in LF. The effectiveness of this approach has been validated in multiple studies. For instance, it has been demonstrated that the migration and differentiation of liver macrophages play a key role in LF, and the C-C chemokine receptor type 8 (CCR8) can effectively limit liver inflammation and the progression of fibrosis.[20] Furthermore, therapeutic strategies targeting LF include the use of anti-TNF-α drugs, which suppress the inflammation driven by TNF-α and exhibit promising antifibrotic effects.[21] For example, etanercept, a genetically engineered fusion protein synthesized from adipose-derived stem cells, significantly reduced the expression of inflammation and fibrosis-related markers in a mouse LF model.[21] These studies suggest that receptor antagonists targeting specific cytokines represent an effective anti-inflammatory approach in the treatment of LF.

Angiogenesis and LF

HSCs also play a crucial role in angiogenesis and the remodeling of the hepatic sinusoidal vasculature. Activated HSCs secrete vascular endothelial growth factor (VEGF) and angiopoietin-1, thereby promoting angiogenesis. Furthermore, their elongated processes extend around the vascular walls, covering the hepatic sinusoidal vessels, and maintaining optimal tight contact with the LSECs. Through paracrine signaling, these cells contribute to vascular contraction and the persistent structural changes in the liver sinusoids, thereby facilitating pathological sinusoidal remodeling.[22] Dysfunction of LSECs leads to hepatic sinusoidal occlusion and increased intrahepatic vascular resistance, promoting the development of portal hypertension and liver cirrhosis.[22] Consequently, HSCs play a dual role in liver angiogenesis and remodeling, acting both as promoters and regulators, making them an important therapeutic target for LF and related diseases. Moreover, the capillarization of hepatic sinusoids and fibrotic scar formation increases resistance to blood flow and oxygen diffusion. This phenomenon is particularly evident during the progression of LF and cirrhosis, resulting in impaired hepatic microcirculation. Disruption of hepatic microcirculation leads to insufficient oxygen supply to the liver, thereby affecting hepatocyte metabolic function. Thus, pathological angiogenesis and hypoxia interfere with normal tissue repair and promote the progression of LF.[23] Therapeutic strategies targeting hepatic sinusoidal capillarization and fibrotic scarring may help to improve liver blood flow and oxygen diffusion, thereby alleviating liver damage and improving patient prognosis.

Immune Microenvironment in LF

The immune microenvironment in LF is a complex network of immune cells that significantly influences the fibrotic process. TAMs exhibit distinct phenotypes, with M1 macrophages promoting inflammation and M2 macrophages contributing to tissue repair and fibrosis resolution.[24] The polarization of TAMs from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype is a critical factor in fibrosis progression. Natural killer (NK) cells play a crucial role in the cytotoxic elimination of activated HSCs, thereby modulating the fibrotic process.[25] Additionally, T cells, particularly CD8+ T cells, are involved in the immune response against fibrosis. However, T cell exhaustion, characterized by the upregulation of inhibitory receptors such as PD-1 and CTLA-4, can impede the immune response and contribute to the persistence of fibrosis.[26] The crosstalk between HSCs and immune cells, including the release of

cytokines and chemokines, further complicates the fibrotic process. Understanding these interactions is essential for developing targeted therapies that can modulate the immune microenvironment to promote fibrosis resolution.

Clinical Progress in the Treatment of LF

There are currently no specific drugs that can directly reverse LF; instead, clinical management hinges on elimination or control of underlying etiologies, lifestyle modification, and meticulous complication management to retard disease progression and enhance patient outcomes. Etiology-directed interventions-such as antiviral regimens that can partially reverse fibrosis in HBV/HCV infection[27] and alcohol abstinence combined with nutritional support to mitigate alcoholic fibrosis-remain foundational.[28] In metabolic associated steatolipodystrophy or NASH, therapeutic emphasis has shifted toward weight reduction, structured exercise, and adjunctive pharmacotherapy with agents such as obeticholic acid or GLP-1 receptor agonists to ameliorate steatosis and inflammation.[29] Moreover, targeted symptomatic management of portal hypertension, ascites, and hepatic encephalopathy-through administration of nonselective β-adrenergic blockers, judicious diuretic regimens, and use of laxatives -is pivotal for improving patient quality of life and forestalling cirrhotic decompensation.[30] Although these conventional approaches can attenuate fibrotic progression to some extent, their one-size-fits-all nature often falls short of addressing the heterogeneity of individual patient needs. In recent years, however, deepened insights into the pathophysiology of LF have catalyzed the discovery of novel therapeutic targets and investigational agents, thereby kindling renewed hope for more efficacious and personalized antifibrotic strategies. The following section introduces the latest clinical drug advances in LF therapy (Table 1). Lanifibranor, a pan-peroxisome proliferator-activated receptor (PPAR) agonist, has demonstrated a dual therapeutic benefit in the Phase IIb NATIVE trial by achieving both histological resolution of NASH and ≥1-stage regression of hepatic fibrosis in affected patients.[31] In the 96-week Phase IIb HARMONY trial, the fibroblast growth factor 21 (FGF21) analog efruxifermin induced a ≥1-stage reduction in fibrosis in 49% of pre-cirrhotic (F2-F3) NASH patients, accompanied by histological resolution of steatohepatitis.[32] Collectively, these innovative antifibrotic target engagements provide robust clinical proof-of-concept to inform future precision-stratified and combination therapy strategies.

Although approaches such as FXR and PPAR agonists, FGF21 analogues, and mesenchymal stem cell therapies have demonstrated antifibrotic potential in multiple clinical trials, they remain hindered by suboptimal target-site delivery and systemic adverse effects. Nanomedicine, by contrast, offers the prospect of exquisitely precise and efficient transport of antifibrotic agents directly to fibrotic loci. To date, the sole nanotherapeutic to reach clinical validation is BMS-986263-a retinoid-conjugated lipid nanoparticle engineered for hepatocyte-stellate cell uptake and controlled release of HSP47-targeting siRNA.[12] In patients with cured chronic hepatitis C and high-grade fibrosis (METAVIR≥F3), a Phase II trial (NCT03420768) showed that 21% of subjects in the 90 mg dose group had an improvement in fibrosis of ≥1 grade, and no serious safety issues were observed.[13] Currently, a phase II study (NCT04267393) has been initiated for patients with compensated NASH cirrhosis;[12] other nanosystems aimed at targeting or gene editing HSCs are still in the preclinical or design stage.

Table 1 Summary of Recent Clinical Investigations of Antifibrotic Agents in LF

Drug	Mechanism of Action	Clinical trial Stage	Ref.
Obeticholic Acid	FXR agonists	Stage III REGENERATE	[33]
Cilofexor	FXR agonists	Stage II NCT02854605	[34]
Lanifibranor	Pan-PPAR agonists	Stage IIb NATIVE	[31]
Selonsertib	ASK1 inhibitors	Stage III STELLAR-3/4	[35]
Cenicriviroc	CCR2/5 antagonists	Stage III AURORA	[36]
Efruxifermin	FGF21 analogs	Stage IIb HARMONY	[32]
Pegbelfermin	PEG-FGF21 analogs	Stage IIb FALCON 2b	[37]
Aldafermin	FGF19 analogs	Stage IIb ALPINE-4	[38]
MSC cell therapy	MSC infusion	Stage I/II/III	[39]

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Applications of Nanomedicines in LF Diagnosis

Early detection of LF is critical for effective treatment; however, many liver diseases present with subtle symptoms in the early stages, often leading to diagnosis at later stages. Currently, LF diagnosis primarily relies on invasive liver biopsy, which may pose certain risks to patients. Fortunately, magnetic resonance imaging (MRI), a high-precision diagnostic tool, has been employed to detect LF.[40] In this context, magnetic nanoparticles play a pivotal role in enhancing the diagnostic accuracy and imaging of LF. For example, Bu et al developed a fibroblast activation protein alpha (FAPα)-responsive MRI molecular probe capable of quantifying LF stages (Figure 2A).[41] The nanoprobe (AFeAGd) consists of

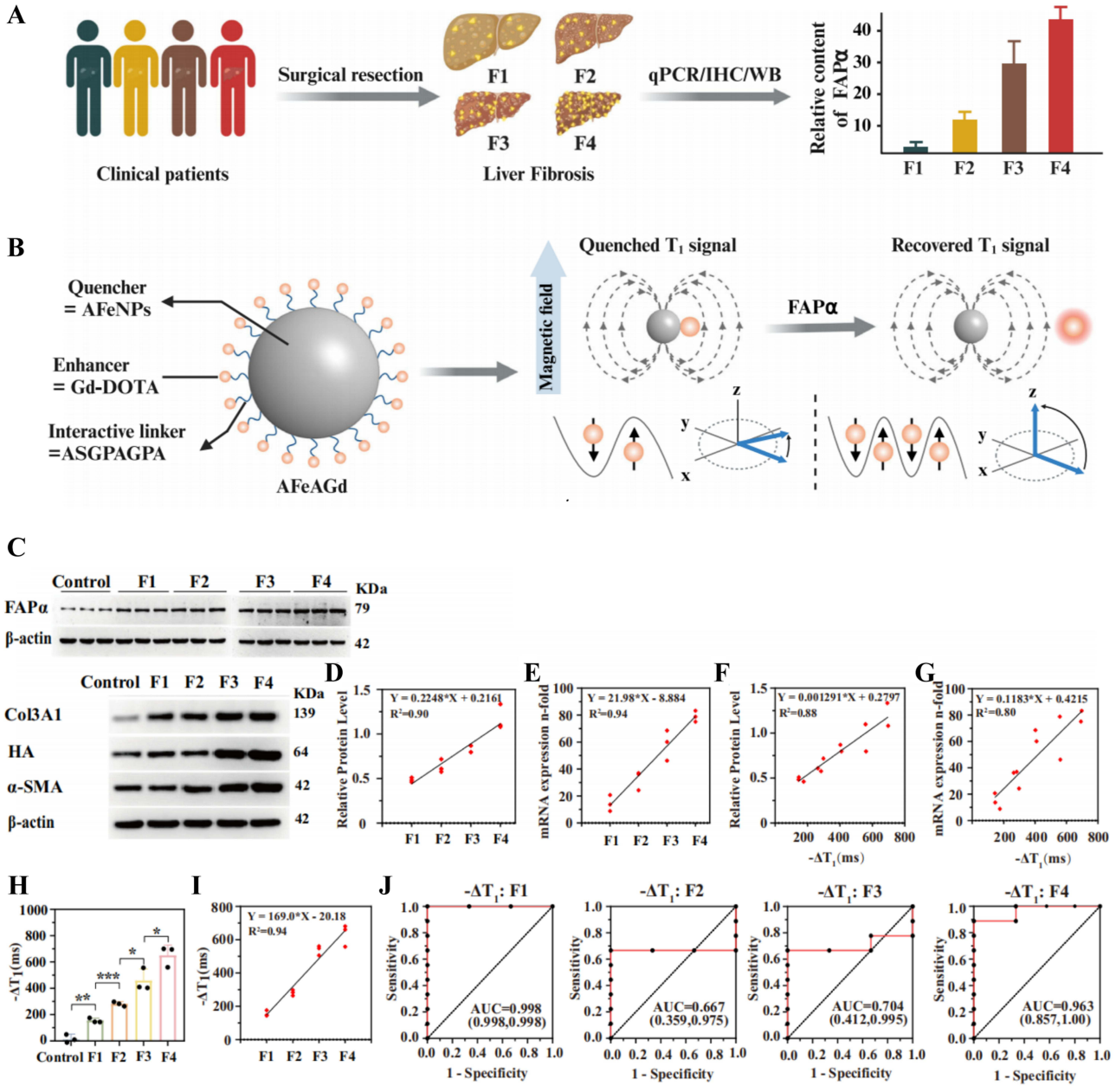

Figure 2 (**A**) Extensive biological validation to screen and identify FAPα as a pathological biomarker for LF grading. (**B**) Schematic diagram of the construction of the AFeAGd nanoprobe. The AFeAGd nanoprobe, based on the MRET effect, exhibits "off/on" T1 MRI signal modulation. (**C**) Western blots for FAPα and additional fibrosis markers (α-SMA, collagen III, and HA) in liver samples. (**D**) Scatter plots showing the linear correlation between each fibrosis marker and fibrosis grade in the Western blot experiments. (**E**) Scatter plots showing the linear correlation between each fibrosis marker and fibrosis grade in the qPCR experiments. Scatter plots of the linear correlation between $-\Delta T_1$ values and FAPα expression at the protein (**F**) and mRNA (**G**) levels in clinical samples. (**H**) Histogram of $-\Delta T_1$ values (n = 3 biological replicates; mean ± SD). (**I**) Scatter plot of the linear correlation between $-\Delta T_1$ values and fibrosis grade biological replicates. (**J**) Receiver operating characteristic (ROC) curves of $-\Delta T_1$ values for distinguishing among F1, F2, F3, and F4 fibrosis grades in clinical samples. Reproduced from Gao J, Wang Y, Meng X, et al. A FAPα-activated MRI nanoprobe for precise grading diagnosis of clinical liver fibrosis. Nature Communications. 2024;15(1):8036. http://creativecommons.org/licenses/by-nc-nd/4.0/.[41]

amorphous iron nanoparticles (AFeNPs) and the clinical T1-MRI contrast agent paramagnetic gadoteric acid (Gd-DOTA) , linked by a FAPα-responsive peptide chain (ASGPAGPA) (Figure 2B). As LF progresses, the increased expression of FAPα triggers cleavage of the ASGPAGPA peptide chain, restoring the T1-MRI signal from Gd-DOTA. Conversely, the signal remains quenched due to the distance-dependent magnetic resonance tuning (MRET) effect between AFeNPs and Gd-DOTA. WB and qPCR results showed that the expression of LF markers such as FAPα protein, Col3A1, HA and α-SMA were significantly different (Figure 2C–I). Receiver operating characteristic (ROC) curve analysis revealed that AFeAGd performs excellently in diagnosing LF stages F1, F2, F3, and F4, with AUC values of 99.8%, 66.7%, 70.4%, and 96.3%, respectively, demonstrating its high efficiency and accuracy in LF staging (Figure 2J). This strategy, utilizing molecular imaging techniques, showcases tremendous potential for early clinical detection and grading of LF. In another study, Balachandran et al synthesized ultra-small (4 nm) heterogeneous iron oxide/dysprosium oxide nanoparticles (IO-DyO NPs) as MRI contrast agents, capable of precisely diagnosing in vivo LF under 7.0T and 9.4T magnetic field strengths.[42] IO-DyO NPs can specifically target the liver and exhibit higher T2 relaxation rates with increasing magnetic field strength. Under ultra-high magnetic fields, IO-DyO NPs significantly enhanced spatial and temporal image resolution and signal-to-noise ratio, enabling precise differentiation between early and moderate stages of LF. MRI diagnostics based on IO-DyO NPs accurately matched liver biopsy results (the clinical gold standard for LF diagnosis), while avoiding the invasiveness of biopsy. This non-invasive approach provides a novel pathway for accurate LF diagnosis, potentially optimizing current diagnostic and therapeutic strategies.

Compared to traditional diagnostic methods, near-infrared fluorescence imaging (NIR) and MRI offer higher sensitivity and excellent spatial resolution, making them effective tools for detecting LF. Li et al synthesized a SPIO@SiO_2–ICG–RGD nanoprobe, which combines superparamagnetic iron oxide (SPIO) nanoparticles, indocyanine green (ICG), and the targeting ligand arginine-glycine-aspartic acid (RGD) to detect LF.[43] In this design, Fe_3O_4 nanoparticles and ICG serve as contrast agents for T2 MRI and NIR imaging, respectively. NIR and MRI imaging results revealed that, compared to normal mice, the liver of fibrotic mice showed significant accumulation of the SPIO@SiO_2–ICG–RGD nanoprobe with markedly enhanced signals, indicating strong targeting ability for fibrotic regions (Figure 3). The SPIO@SiO_2–ICG–RGD nanoprobe enabled both qualitative and quantitative evaluation of LF,

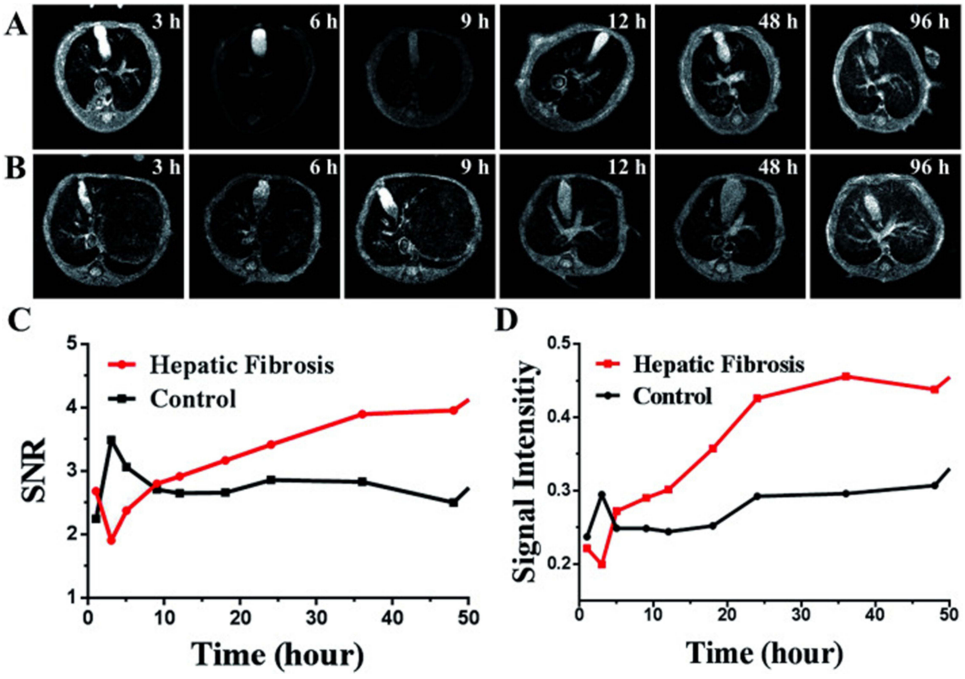

Figure 3 Comparison of MRI signals between SPIO@SiO_2-ICG-RGD in LF mice and healthy mice: (**A**) LF model; (**B**) Healthy control group; (**C** and **D**) Comparison of MRI signal intensity between the two groups. Reproduced from Li Y-F, Shang W, Liang X, et al. The diagnosis of hepatic fibrosis by magnetic resonance and near-infrared imaging using dual-modality nanoparticles. RSC Advances. 2018;8(12):6699–6708. https://creativecommons.org/licenses/by/3.0/.[43]

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accurately identifying fibrotic areas in the liver. In terms of qualitative assessment, the probe specifically binds to the integrin αvβ3 receptor on the surface of activated HSCs via the RGD peptide. In vitro experiments show a significantly enhanced near-infrared fluorescence signal in HSCs, while normal hepatocytes exhibit weaker signals. In vivo experiments reveal that the liver fluorescence signal in HF mice lasts longer and the target-to-background ratio is significantly higher than that in healthy controls. Prussian blue staining further confirms the enrichment of iron ions from the probe in fibrotic livers. Quantitative assessment is achieved through dual-modality MRI and NIR imaging: The T_2-weighted signal intensity in MRI gradually decreases after probe injection, with signal changes correlating with the degree of fibrosis. In NIR imaging, the fluorescence signal intensity and pharmacokinetic parameters (such as mean fluorescence intensity) in the HF group can be used to quantify fibrosis progression.

This bimodal imaging technique, which integrates the advantages of MRI and NIR imaging, not only significantly improves the sensitivity of LF detection but also provides precise structural and functional information, facilitating a comprehensive assessment of LF. This approach holds significant potential for clinical applications.

In recent years, fluorescence imaging-owing to its high sensitivity, noninvasiveness, and excellent tissue penetration-has shown tremendous promise for the early diagnosis and dynamic monitoring of LF. Wang et al developed a silica cross-linked micelle nanosystem targeted to the C-X-C motif chemokine receptor 4 (CXCR4).[44] By loading an $ONOO^-$-responsive fluorescent probe and co-delivering two antifibrotic drugs, this platform achieves an integrated theranostic approach for early "diagnosis + treatment" of LF. Zhang et al reported an activatable near-infrared fluorescence/photoacoustic dual-mode probe (hCy-Tf-CA), which uses taurine for liver targeting and, upon reaction with superoxide anions, simultaneously generates both fluorescence and photoacoustic signals.[45] In models of acute liver injury (AILI) and autoimmune hepatitis (AIH) in mice, this probe provided high-signal-to-noise in situ imaging suitable for early detection and real-time monitoring of hepatic inflammation. Additionally, another study designed two red-emissive two-photon probes (TPCN1 and TPCO2) and, based on TPCO2, constructed a nitroreductase-responsive (NTR)- probe (TPCO-NO2).[46] This probe discriminates varying intracellular NTR levels under different hypoxic conditions and sensitively images hypoxia during LF in vivo, making it highly valuable for early diagnosis and therapeutic evaluation of fibrosis.

In addition to MRI and fluorescence imaging, ultrasound molecular imaging technology has also garnered significant attention. Xuan et al developed a targeted peptide-based ultrasound contrast agent, which is coated with Poly(lactic-co-glycolic acid) (PLGA) and functionalized with cyclic RGD peptides on the core-shell structured nanoparticles.[47] This contrast agent enables high-contrast imaging between LF regions and adjacent tissues during ultrasound imaging, allowing for non-invasive and precise evaluation of LF severity. It shows promise for early, non-invasive diagnosis of LF.

Compared to traditional diagnostic methods, MRI, NIR, and ultrasound molecular imaging each exhibit distinct advantages and limitations in detecting LF. Table 2 summarizes the imaging principles, clinical applications, and technical highlights of these three modalities. For instance, MRI provides high - resolution quantitative staging, while ultrasound offers real - time dynamic imaging at a lower cost. On the other hand, NIR combines sensitivity with dual -

Table 2 Comparative Analysis of Diagnostic Methods for LF: Imaging Principles, Advantages, and Clinical Applications

Diagnostic Methods	Imaging Principles	Advantages	Limitations	Clinical Applications
MRI	Magnetic Resonance Imaging	High precision, multiparametric imaging, radiation - free, high soft - tissue contrast	Expensive equipment, reliant on high - end hardware	LF staging (F1 - F4), early diagnosis
NIR	Near - infrared fluorescence imaging	High sensitivity, high spatial resolution, real - time dynamic imaging	Limited tissue penetration depth (suitable for superficial or specific areas)	Early detection of LF, dual - modality imaging (combined with MRI)
Ultrasound molecular imaging technology	Ultrasound combined with targeted nanoparticle contrast agents	Real - time dynamic imaging, non - invasive, portable, low - cost	Lower resolution (micron - level), signal attenuation in deep tissues	Early non - invasive diagnosis, real - time assessment of fibrosis severity

modality imaging capabilities through SPIO@SiO2–ICG–RGD probes. These complementary features highlight their potential synergies in clinical practice.

Applications of Nanomedicines in LF

In recent years, the development of nanoparticles has predominantly focused on creating drug delivery systems that target LF tissues. These targeted drug delivery systems can be categorized into two main types based on their targeting mechanisms: passive targeting and active targeting. Passive targeting relies on the physicochemical properties of the drug delivery system (such as particle size, surface charge, etc.) and utilizes the enhanced permeability and retention (EPR) effect to enable the spontaneous accumulation of drugs in diseased tissue areas. In contrast, active targeting involves the functionalization of nanoparticles with specific targeting ligands (such as peptides, antibodies, etc.) on their surface, allowing for selective binding with receptors on the target cell surface. This significantly enhances the targeting efficiency and delivery of drugs. Strategies combining active and passive targeting enable precise regulation of nanoparticle distribution and accumulation in vivo, thereby allowing for efficient targeting of specific cell types. Moreover, the ability of nanoparticles to respond to physiological stimuli (such as pH, ROS, or overexpressed enzymes) is particularly relevant in intracellular drug release mechanisms. This responsiveness not only enhances the drug's targeting and efficacy but also reduces side effects in normal tissues. Nanoparticles can trigger drug release under specific physiological conditions, and in the context of LF treatment, they can respond to particular sHSCtimuli within the LF microenvironment, ensuring precise drug release and improving drug accumulation and efficacy in the fibrotic region.

Passive Targeting Strategy

Passive targeting in LF relies on the EPR effect, driven by nanoparticle physicochemical properties and pathological tissue characteristics. For polymeric micelles such as the CRM/NIL system developed by Fan et al, passive targeting is achieved through precise control of particle size and surface charge.[48] The CRM/NIL micelles exhibited a hydrodynamic diameter of 217.0 ± 8.1 nm as measured by dynamic light scattering (DLS), which falls within the optimal range (10–200 nm) for extravasation through the enlarged fenestrations (200–800 nm) of fibrotic liver sinusoids.[48] Notably, the smaller dried-state diameter (87.6 ± 8.3 nm via TEM) reflects structural compactness, while the hydrated size ensures prolonged circulation.[48] The surface charge of −16.55 ± 2.92 mV, attributed to collagenase I grafting, minimizes opsonization by serum proteins and facilitates penetration through the negatively charged sinusoidal glycocalyx.[48] Combined with a PEG shell that maintains stability in serum for over 3 days, these properties enable sustained EPR-mediated accumulation in fibrotic regions, further enhanced by collagenase-mediated degradation of collagen barriers.[48]

Similarly, choline-modified lipid nanoparticles (CP-LNPs) described by Wang et al demonstrate passive targeting through tailored surface properties.[49] Unmodified control LNPs (Ctrl-LNPs) exhibited a negative charge (−21 mV), whereas CP incorporation reversed the surface charge to a positive range (+17 to +23 mV) depending on the doping ratio.[49] This charge reversal enhances interactions with negatively charged cell membranes in fibrotic tissue while avoiding rapid renal clearance.[49] Despite charge modifications, CP-LNPs maintained a consistent hydrodynamic diameter (~100–120 nm), balancing vascular extravasation via EPR and deep tissue penetration.[49] Intravenous administration resulted in near-complete liver accumulation (>95%) within 10 minutes, leveraging the leaky vasculature and impaired lymphatic drainage characteristic of fibrotic livers.[49] The PEGylated surface further reduced nonspecific interactions, highlighting how size stability and charge optimization synergistically enhance EPR-driven targeting.[49] CP-LNPs achieve rapid liver accumulation, effective colocalization with mitochondria, time-dependent enhancement, and mitigation of mitochondrial dysfunction in a LF model via passive targeting mechanisms (Figure 4A–D).

These examples underscore three critical determinants of passive targeting: 1) Nanoparticle size (10–200 nm by DLS) to match vascular fenestration sizes in fibrotic liver; 2) Surface charge modulation (−20 to +30 mV) to balance circulation stability and tissue penetration; and 3) Pathological amplification of EPR through disrupted endothelial architecture (200–800 nm pores) and compromised lymphatic function. Together, these factors enable nanocarriers to exploit disease-specific microenvironments for targeted drug delivery.

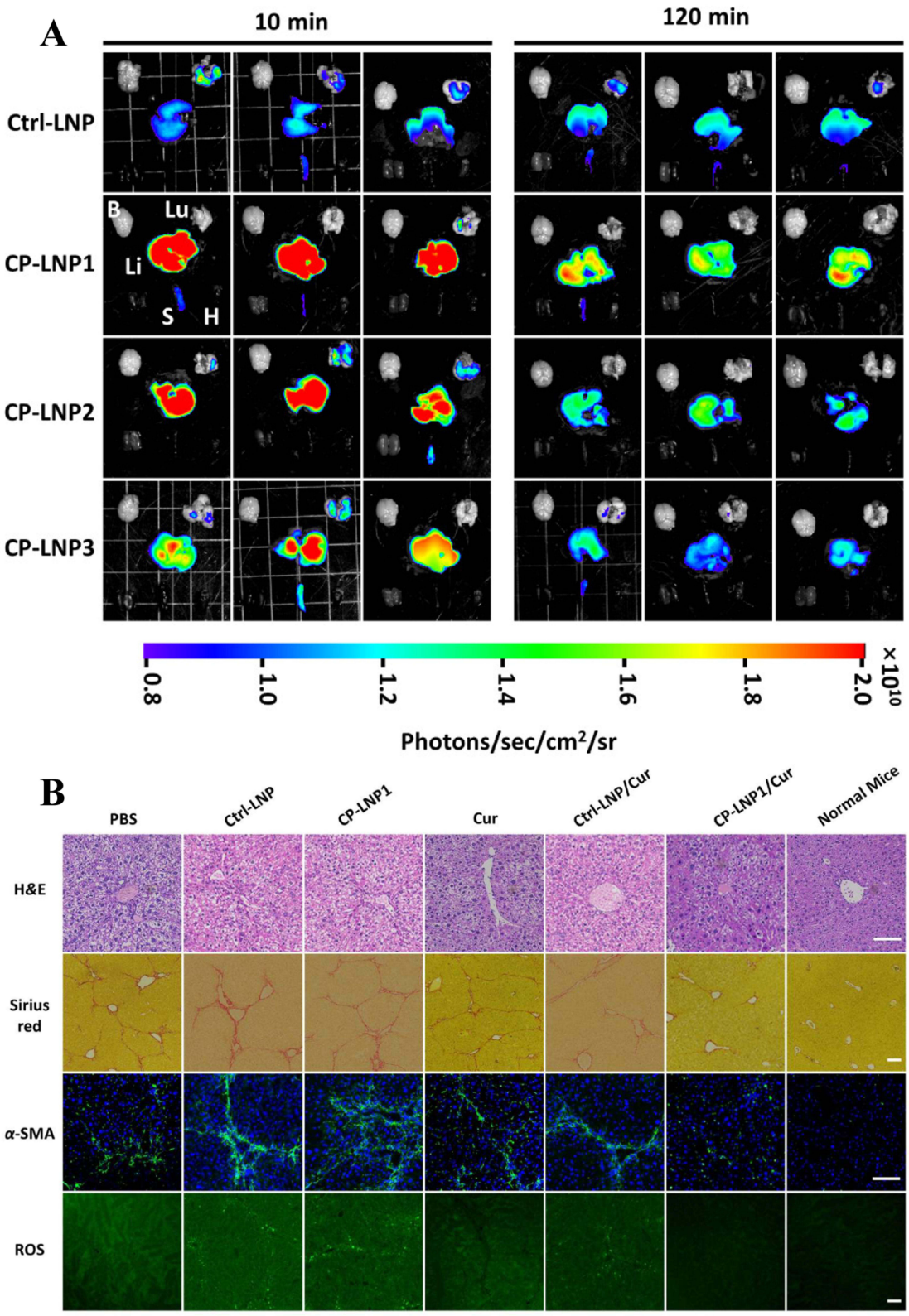

Figure 4 (**A**) In vivo near-infrared fluorescence imaging of major organs collected from normal mice after intravenous injection of DiD-labeled CP-LNPs at 10 and 120 minutes. (**B**) Images of HPC3&E, Sirius Red, α-SMA staining, and ROS assays of excised livers from different treatment groups. Scale Bar, 50 μm. Reprinted with permission from Yuan K, Lai K, Miao G, et al. Cholinized-Polymer Functionalized Lipid-Based Drug Carriers Facilitate Liver Fibrosis Therapy via Ultrafast Liver-Targeting Delivery. Biomacromolecules. 2024;25(10):6526–6538. Copyright © 2025 American Chemical Society.[49]

Table 3 Specific Receptors for Targeting HSCs

HSC-Specific Receptor	Targeted Ligand	Drug	Carrier	Reference
IGFII	M6P	Y27632	Conjugate	[51]
PDGFRβ	PDGFRβ-antibody	PDGFRβ-antibody	Gold nanorods	[52]
RBP	Vitamin A	Camptothecin	Polymeric micelles	[53]
	Vitamin A	Pirfenidone	Liposomes	[54]
Integrins αvβ3	cRGD	IFN-α1b	Liposomes	[55]
CD44	Chondroitin Sulfate	Vismodegib	Multifunctional Nanoparticles	[56]
	Hyaluronic acid	Bilirubin	Nanoparticles	[57]

Active Targeting Strategies

Active targeting drug delivery systems achieve precise recognition and binding to specific receptors expressed in LF by functionalizing the surface of nanocarriers with specific targeting ligands, such as peptides, antibodies, or small molecules (Table 3). These receptors, typically overexpressed or upregulated during the progression of LF, include integrin αvβ3, IGF-II receptor (IGFII-R), PDGFRβ, retinol-binding protein receptor, and CD44 receptor, among others (Figure 5). These receptors play critical roles in the activation, proliferation, migration, and survival of HSCs, making them promising targets for nanoparticle-based therapies.[50]

Targeting the IGFII-R

The IGFII-R, a multifunctional receptor expressed on HSCs, is highly and specifically upregulated on activated HSCs during LF. A study designed a liposomal system functionalized with human serum albumin (HSA) conjugated to mannose-6-phosphate (M6P) for targeting HSCs through the M6P receptor.[58] The system delivered the Rho kinase inhibitor Y27632, which suppresses HSCs activation and reduces ECM synthesis by inhibiting the Rho-kinase signaling pathway. The conjugate of M6P-HSA and Y27632 displayed excellent liver-targeting capability by accumulating in liver tissue and effectively targeting HSCs.[51] Compared to free Y27632, the cell-specific conjugate more efficiently inhibited HSCs activation, significantly reduced hepatic collagen deposition and serum damage biomarkers, and alleviated LF. M6P has been extensively utilized in the delivery systems of liposomes, micelles, and serum albumin nanoparticles, demonstrating significant therapeutic efficacy in LF treatment.

Targeting PDGFRβ

The PDGF receptor is a tyrosine kinase receptor involved in critical biological processes such as cell proliferation, migration, differentiation, and angiogenesis. PDGFR has two isoforms, PDGFRα and PDGFRβ, with the latter being highly expressed in LF. PDGFRβ is a key receptor in HSCs activation, promoting HSCs proliferation and migration upon ligand binding. This activity exacerbates ECM synthesis and deposition, thereby advancing the fibrotic process.[59] Targeting PDGFRβ presents a promising therapeutic strategy for LF intervention. Studies have demonstrated that

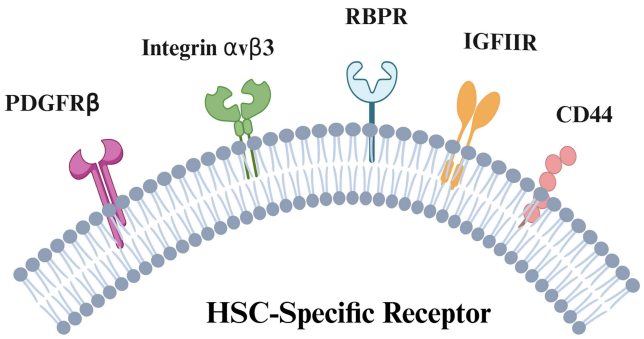

Figure 5 Overexpressed receptors in activated HSCs: IGF-II receptor; integrin αvβ3 receptor; PDGFRβ; retinol-binding protein receptor (RBPR); CD44 receptor. Created in BioRender. Niu, R. (2025) https://BioRender.com/dn3ieir.

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inhibiting PDGFRβ signaling effectively suppresses HSCs activation, reduces ECM production, and consequently slows or even reverses the progression of LF. Gold nanorods (GNRs) are advantageous due to their passive accumulation in the liver, enhancing targeting efficiency. Additionally, their photothermal properties, when combined with specific cell delivery mechanisms, make them suitable for localized photothermal ablation therapy. Ribera et al developed GNR-PDGFRβ to selectively target and disrupt activated HSCs in fibrotic regions through plasmonic photothermal therapy (PPTT), thereby reversing LF.[52] Their study showed significantly enhanced luminescence signals in fibrotic livers compared to healthy tissues 10 days post-treatment, indicating efficient accumulation and excellent targeting by the nanorods (Figure 6A and B). Furthermore, in comparison to other experimental groups, the PDGFRβ and PPTT treatment group exhibited a marked reduction in α-SMA-positive cells and liver damage biomarkers, highlighting the efficacy of GNR-mediated photothermal therapy in mitigating liver inflammation and cell damage and reversing LF in mouse models (Figure 6C and D).

Targeting Retinol-Binding Protein Receptor (RBPR)

HSCs, located in the perisinusoidal space, serve as the primary storage site for retinol, absorbing and storing approximately 80% of the body's retinol under quiescent conditions. RBPR is overexpressed in HSCs, and its interaction with retinol plays a regulatory role in HSCs activation, as well as the synthesis and deposition of the ECM.[60] Consequently, retinol and its derivatives have been utilized as targeting ligands in nanomedicines to achieve precise drug delivery to activated HSCs.[61] For example, Li et al developed polymeric micelles functionalized with vitamin A-derived camptothecin (CPT), which specifically target HSCs.[53] These micelles selectively inhibit the expression of hypoxia-inducible factor-1α and glycolysis in HSCs, ultimately suppressing LF. Similarly, Qin et al designed vitamin A (VA)-modified lipid nanoparticles, where the surface-modified VA efficiently recognizes and binds to the RBPR overexpressed on HSCs.[54] This system significantly increases the local drug concentration in fibrotic regions. In vivo studies demonstrated that these lipid nanoparticles effectively reduced liver damage and alleviated fibrosis, showing promising therapeutic outcomes and offering a novel solution for the precise treatment of LF.

Targeting Integrin αvβ3 Receptor

Integrin αvβ3 functions as a receptor for various adhesion proteins, including fibronectin and type VI collagen, facilitating interactions between ECM and cells. It plays a critical role in biological processes such as cell adhesion, migration, proliferation, and signal transduction.[62] During LF, the expression of αvβ3 receptors is upregulated, promoting the activation and proliferation of HSCs and driving fibrosis progression. Both integrins and adhesion proteins in the ECM contain the arginine-glycine-aspartic acid (RGD) peptide sequence.[63] Activated HSCs recognize the RGD sequence within matrix molecules through integrins, thereby regulating fibrotic formation. This interaction has been extensively exploited in the design of HSC-targeting nanomedicines. For instance, Du et al modified cyclic RGD peptides (cRGD) onto sterically stabilized liposomes (SSLs), creating a novel delivery platform, cRGD-SSL, capable of targeting interferon-α1b (IFN-α1b) to HSCs.[55] These liposomes significantly enhanced the concentration of IFN-α1b in fibrotic regions, effectively suppressing HSCs activation and excessive ECM deposition, thereby alleviating fibrosis. This targeted delivery system offers a promising precision-based strategy for the treatment of LF.

Targeting CD44 Receptor

CD44 is a cell adhesion molecule highly expressed on the surface of HSCs and other hepatic cells. It interacts with ligands such as hyaluronic acid (HA) and chondroitin sulfate (CS), which are commonly employed in designing HSC-targeted drug delivery systems. Li et al developed CCR nanoparticles composed of CREKA (a specific fibronectin ligand) and chondroitin sulfate, co-loaded with retinoic acid (a Golgi apparatus disruptor) and vismodegib (a hedgehog pathway inhibitor).[56] These CCR nanoparticles specifically target activated HSCs, accumulate in the Golgi apparatus, and disrupt its structure and function, while simultaneously inhibiting the hedgehog signaling pathway. This dual mechanism significantly suppressed HSCs activation and ECM secretion, demonstrating synergistic anti-fibrotic therapeutic potential. Similarly, Shinn et al formulated hyaluronic acid-bilirubin nanoparticles (HABNs) designed to specifically target the CD44 receptor.[57] Intravenous administration of HABNs effectively targeted activated HSCs in a mouse model of LF,

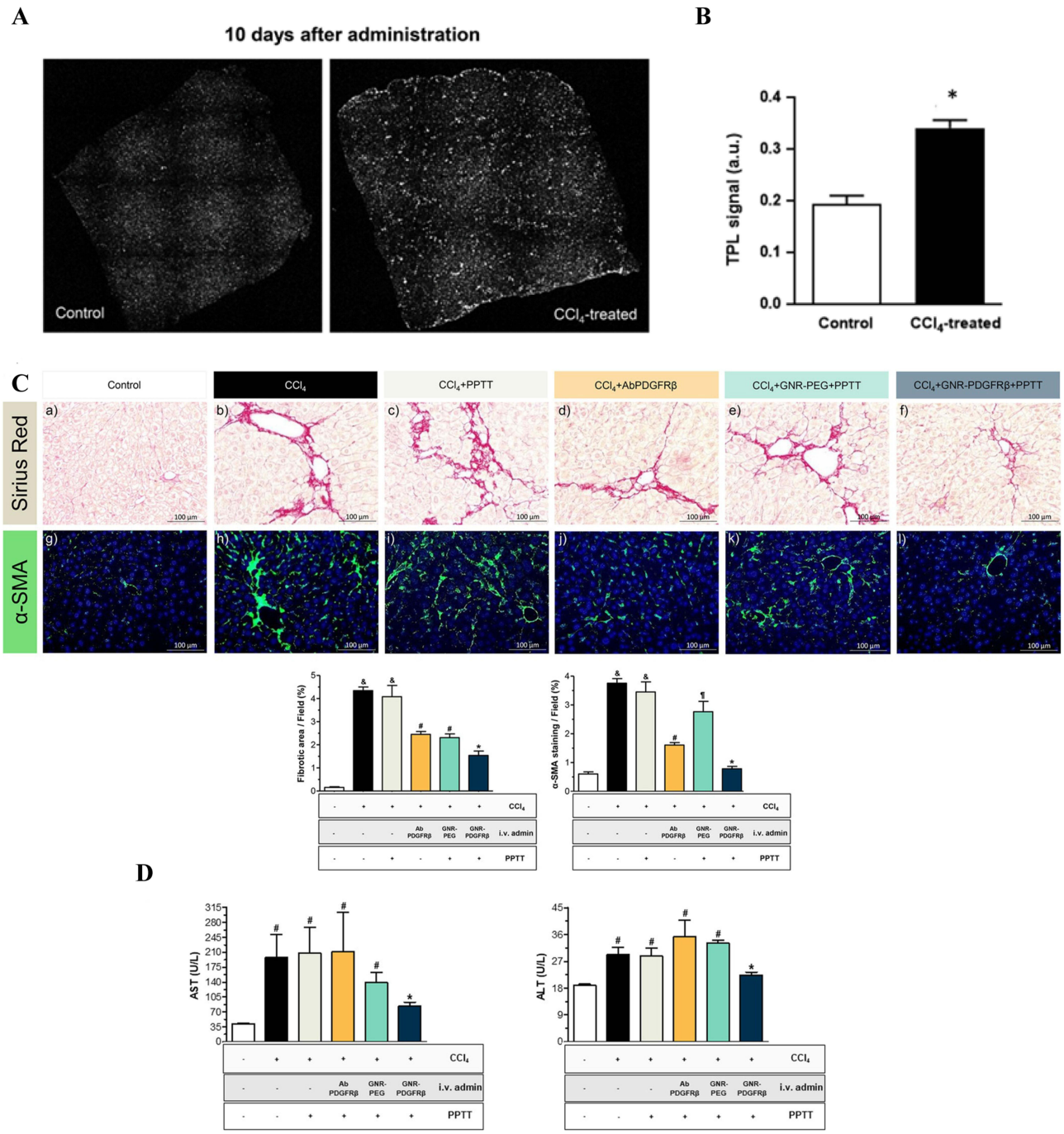

Figure 6 (**A**) Representative TPL (two-photon polymerization lithography) images of liver tissue sections from healthy and LF mice, 10 days after injection with GNR-PDGFRβ. (**B**) Quantitative analysis of the TPL signal of GNR-PDGFRβ in liver tissue sections. (n = 4 each group, * indicates statistical differences compared to control mice, with $p < 0.0005$). (**C**) Liver tissue sections from different treatment groups of mice, stained with Sirius Red (red) and immunostained with anti-α-SMA antibody (green). The lower panel shows the quantification of fibrosis areas and the percentage of α-SMA-positive cells using computer-assisted techniques. Computer-assisted quantification for the percentages of both fibrotic area and αSMA is shown in the bottom graphs; bars represent the mean ± SEM. Fibrotic area: and $p < 0.01$ vs control mice, #$p < 0.01$ vs control mice, CCl4 mice and CCl4 + PPTT, and *$p < 0.01$ vs control mice, CCl4 mice, CCl4 + PPTT, CCl4 + AbPDGFRβ, and CCl4 + GNR-PEG + PPTT. αSMA: and $p < 0.01$ vs control mice and CCl4 + AbPDGFRβ, #$p < 0.01$ vs control mice and CCl4 + GNR-PEG + PPTT, ¶$p < 0.05$ vs CCl4 mice, and *$p < 0.01$ vs CCl4 mice, CCl4 + PPTT, CCl4 + AbPDGFRβ, and CCl4 + GNR-PEG + PPTT (n = 15). (**D**) Blood levels of AST and ALT in different experimental groups. Reproduced with permission from reference. Bars represent the mean ± SEM. AST: #$p < 0.05$ vs control mice, and *$p < 0.05$ vs control mice, CCl4 mice, CCl4 + PPTT, CCl4 + AbPDGFRβ, CCl4 + GNR-PEG + PPTT and CCl4 + GNR-PDGFRβ + PPTT. ALT: #$p < 0.01$ vs control mice, and *$p < 0.01$ vs CCl4 mice, CCl4 + PPTT, CCl4 + AbPDGFRβ and CCl4 + GNR-PEG + PPTT (n = 15). Reprinted with permission from Ribera J, Vilches C, Sanz V, et al. Treatment of Hepatic Fibrosis in Mice Based on Targeted Plasmonic Hyperthermia. ACS Nano. 2021;15 (4):7547–7562. Copyright © 2025 American Chemical Society.[52]

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inhibiting their activation, proliferation, and collagen production. This approach demonstrated a significant capability to prevent the progression of LF, offering a promising therapeutic strategy.

Mediating Immune Regulation

The development of LF is closely related to the disorder of the hepatic immune microenvironment, making immune regulation therapy one of the important strategies for reversing LF.[64] Nanomedicines, with their unique physicochemical properties, can achieve precise targeting of immune cells and regulation of immune responses, thus showing great potential in the immune therapy of LF.[65]

Immune Cell Targeting and Polarization Regulation

Nanomedicines can achieve precise targeting of hepatic immune cells (such as macrophages, T cells, and NK cells) through surface modification with specific targeting ligands.[66] For example, TAMs play a dual role in LF.[67] Similarly, nanomedicines targeting T cells can modulate the functional state of T cells, reducing T cell exhaustion and enhancing their immune response to fibrosis-related antigens.[68]

Nanomedicine-Based Immune Checkpoint Regulation

Immune checkpoint molecules (such as PD-1, CTLA-4, etc.) play an important role in the persistence and progression of LF. Nanomedicines can precisely block these molecules by carrying immune checkpoint inhibitors. For example, the combination of anti-PD-1 antibodies with nanocarriers can enhance their enrichment in the liver, improve therapeutic efficacy, and reduce the risk of systemic immune reactions.[69] In addition, nanomedicines can also co-deliver immune checkpoint inhibitors with anti-fibrotic drugs to achieve synergistic effects of immune regulation and direct anti-fibrotic treatment.[69]

Mechanisms of Nanomedicine-Mediated Immune Regulation

Nanomedicines can regulate the immune system through various mechanisms. On one hand, nanomedicines can alleviate hepatic inflammation by modulating the signaling pathways of immune cells, such as inhibiting the production of pro-inflammatory cytokines and activating anti-inflammatory signaling pathways.[70] On the other hand, nanomedicines can also influence the metabolic state of immune cells to regulate their function and phenotype. For example, certain nanomedicines can modulate the metabolic reprogramming of macrophages, promoting their shift to an anti-inflammatory phenotype, thereby inhibiting the progression of LF.[71]

Combination Delivery Strategies

LF is characterized by complex pathological features and diverse etiologies, making it challenging to achieve optimal therapeutic outcomes with monotherapy. Consequently, combination drug delivery systems have garnered increasing attention for LF treatment. These systems enable the simultaneous delivery of multiple drugs targeting different pathological mechanisms of LF, thereby significantly enhancing therapeutic efficacy.[72] SOR, a TGF-β1/Smad3 signaling inhibitor, has demonstrated a strong inhibitory effect on HSCs activation and proliferation in vitro.[73] Glycyrrhetinic acid (GA), a hydrophobic compound extracted from herbal medicine, has shown promising results in LF treatment.[74] Zhou et al designed collagenase I (COL)-modified glycyrrhetinic acid-hyaluronic acid (GA-HA) copolymer prodrugs encapsulating SOR into S/CHG micelles to enhance ECM degradation and HSCs targeting for LF therapy (Figure 7).[75] The S/CHG micelles effectively degraded fibrotic ECM via COL activity and exhibited superior HSCs internalization capabilities. Additionally, intracellular esterases accelerated the release of SOR and GA from the micelles, facilitating higher drug accumulation in fibrotic liver tissue and significantly improving targeting efficiency toward activated HSCs. More importantly, the S/CHG micelles reduced collagen deposition, inhibited HSCs activation, and downregulated fibrosis-associated factors. By leveraging multiple mechanisms-including anti-angiogenesis, modulation of the LF microenvironment, and inhibition of epithelial-mesenchymal transition-they effectively reversed LF. In conclusion, multifunctional nanocarrier-based combination delivery systems offer a promising strategy for the treatment of LF.

Furthermore, with the advancement of gene therapy technologies, combination strategies for LF treatment, particularly those incorporating gene therapy, have emerged as a research hotspot, demonstrating significant potential for

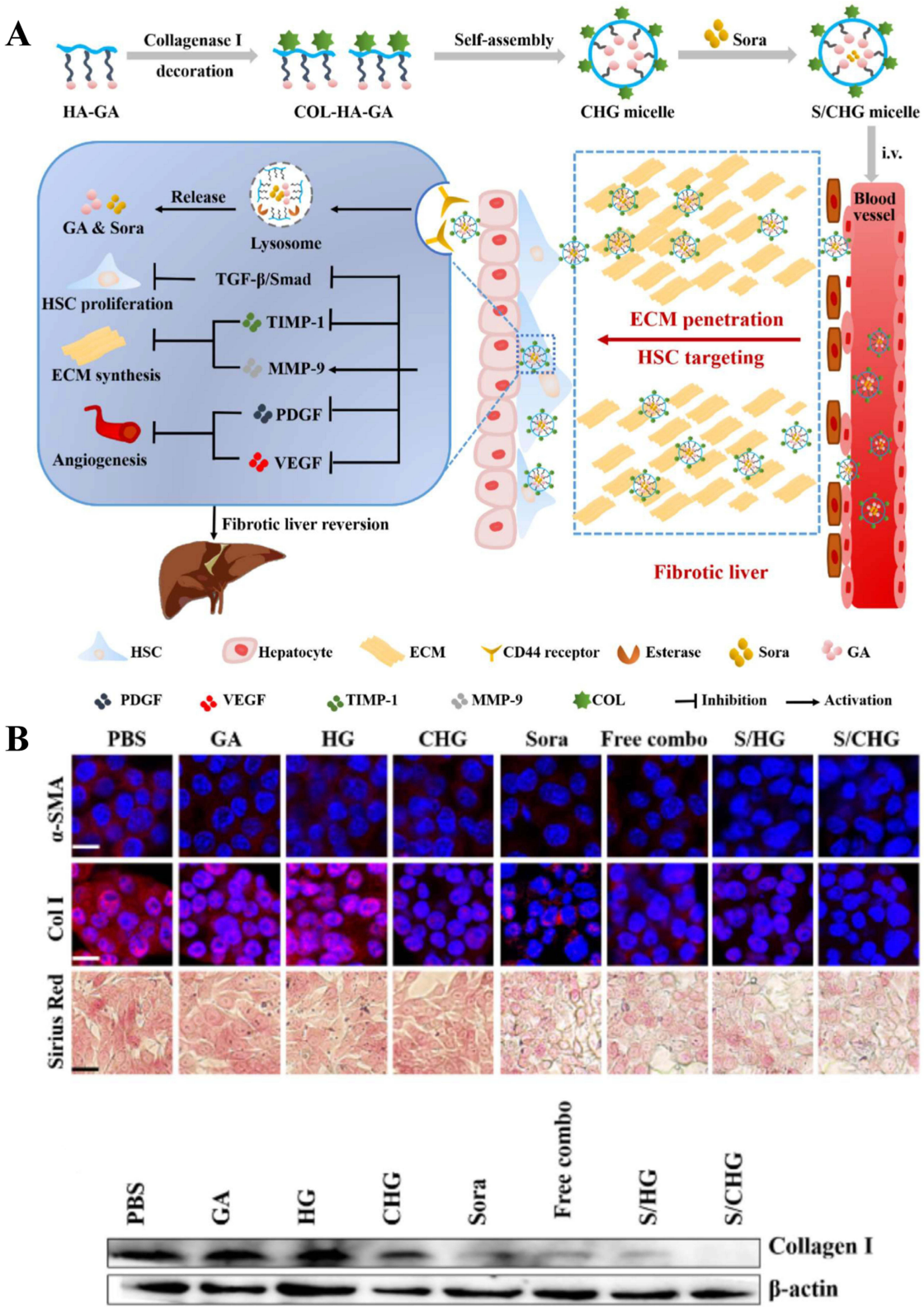

Figure 7 (**A**) Schematic diagram of COL-modified HA-GA micelles co-delivering SOR. (**B**) α-SMA, collagen I and Sirius Red stainings of activated HSCs with various formulation treatments. Scale bar = 20 μm. (**C**) Collagen I expression in HSCs assayed by Western blot. Reprinted from Acta Biomaterialia, 152, Zhou L, Liang Q, Li Y, et al. Collagenase-I decorated co-delivery micelles potentiate extracellular matrix degradation and hepatic stellate cell targeting for liver fibrosis therapy. 235-254, Copyright 2022, with permission from Elsevier.[75]

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clinical translation. Pirfenidone (PFD) has shown promise in combating LF, with studies confirming its efficacy in treating CCl_4-induced LF in rats by inhibiting HSCs activation and collagen synthesis.[76,77] Additionally, small interfering RNA (siRNA) offers the potential to target and suppress fibrosis-associated genes, thereby effectively inhibiting HSCs activation. In one study, researchers developed vitamin A (VA)-modified zeolitic imidazolate framework-8 (ZIF-8) lipid nanoparticles (GP@ZIF-VL) to simultaneously deliver the antifibrotic agent pirfenidone and a genetic therapeutic agent (siRNA).[78] This dual-functional nanoparticle system targeted activated HSCs, achieving synergistic inhibition of HSCs activation through chemical and genetic modulation of fibrosis-related gene expression (Figure 8).

Building on this strategy, the investigators co-encapsulated a structure-guided endonuclease (SGN) and the small--molecule drug rosiglitazone within ~40 nm nanomicelles.[79] The confinement of both components inside the nanomicelle

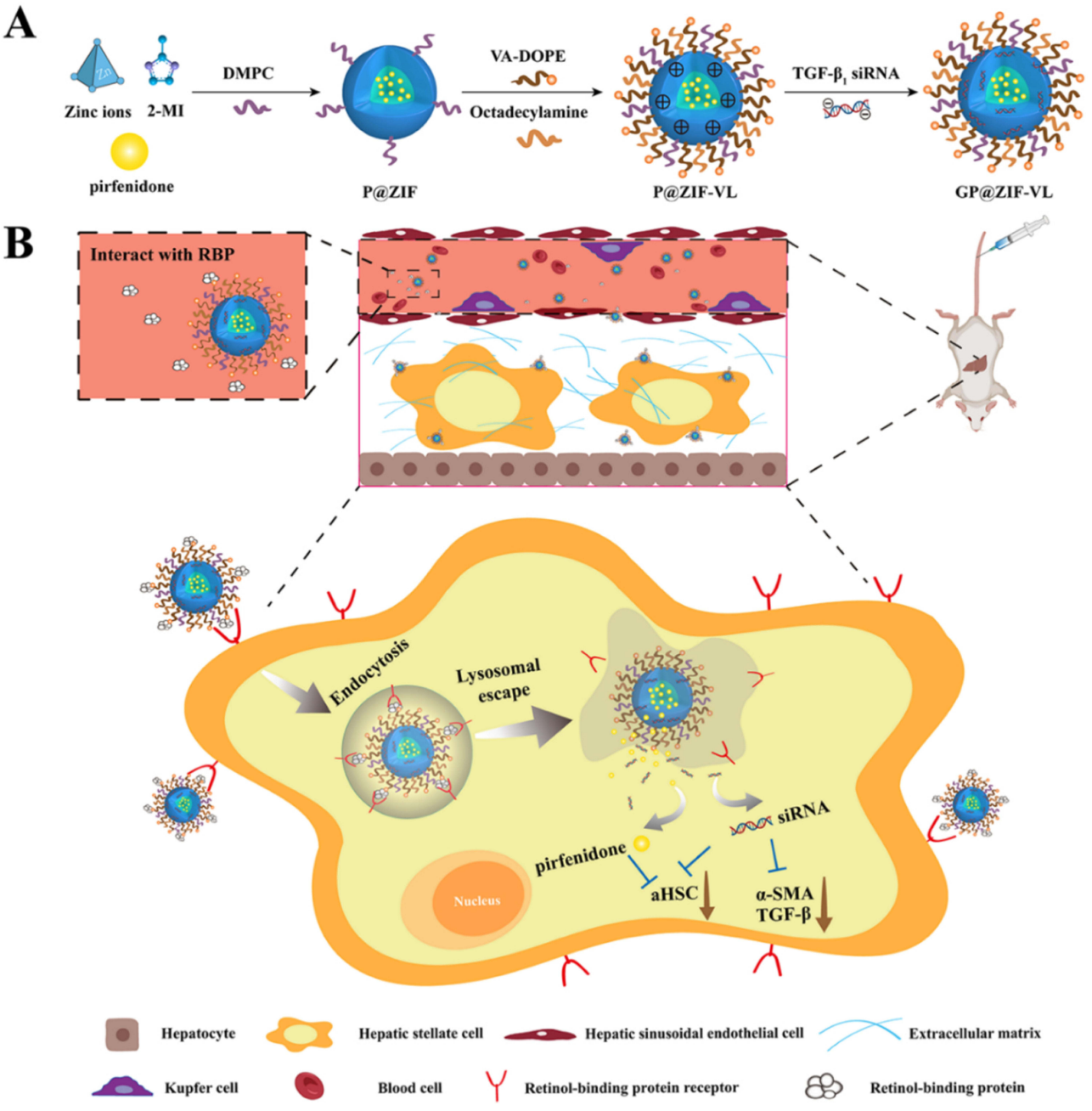

Figure 8 (**A**) Synthesis process of GP@ZIF-VL nanocomposite. (**B**) Schematic illustration of GP@ZIF-VL nanocomposite-mediated chemical-gene synergistic therapy targeting HSCs to inhibit HSC activation and treat LF. Reprinted from Colloids and Surfaces B: Biointerfaces, 231, Wang K, Chen H, Qin S, et al. Co-delivery of pirfenidone and siRNA in ZIF-based nanoparticles for dual inhibition of hepatic stellate cell activation in liver fibrotic therapy. 113567, Copyright 2023, with permission from Elsevier.[78]

produces a "space-induced acceleration" effect that markedly enhances mRNA-targeted cleavage efficiency. In vivo, this dual-delivery system successfully reverses LF in mice by simultaneously promoting collagen degradation and inhibiting collagen synthesis.

These combined drug delivery strategies not only enhanced drug bioavailability and reduced systemic toxicity but also improved therapeutic efficacy by specifically targeting activated HSCs. Such innovative approaches highlight the tremendous potential for advancing LF therapy, paving the way for more effective antifibrotic treatments in the future.[80]

Smart Responsive Delivery Strategies

Nanoparticles that respond to physiological stimuli such as pH, ROS, or overexpressed enzymes have gained considerable attention for their applications in intracellular drug release mechanisms. These systems not only enhance drug targeting and therapeutic efficacy but also reduce off-target effects on normal tissues.[81] In the context of LF treatment, nanoparticles can be engineered to respond to specific physiological cues within the fibrotic microenvironment, enabling precise drug release, enhanced accumulation at fibrotic sites, and improved therapeutic outcomes.

Acidic pH-Responsive Systems

The acidic nature of the LF microenvironment presents an opportunity for targeted drug delivery. Exploiting this characteristic, researchers have developed various nanocarriers capable of releasing drugs under specific pH conditions to improve bioavailability and therapeutic outcomes. For instance, Lin et al designed polydatin-loaded micelles (PD-MC) based on an amphiphilic block copolymer comprising polyethylene glycol (PEG) and poly(2-(((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)benzyl)oxy)carbonyl)oxy)ethyl methacrylate co 2-(diisopropyl amino)ethyl methacrylate) (P (PBEM-co-DPA)).[82] These micelles exhibit dual sensitivity to ROS and pH, making them highly effective for LF treatment. The hydrophobic PPBEM core of the micelle reacts with ROS, triggering drug release and mitigating oxidative stress associated with LF. Additionally, the PDPA segments confer pH sensitivity, enabling polydatin release in the acidic lysosomal environment (pH 4.5–5.5) within cells (Figure 9A–C). Studies demonstrated that PD-MC accumulates significantly in the liver of CCl_4-induced LF mice compared to healthy controls (Figure 9D and E). Collectively, PD-MC not only facilitates efficient hepatic delivery of polydatin but also enables microenvironment-responsive drug release, effectively targeting multiple hepatic cell types involved in fibrosis. In vitro and in vivo findings revealed that PD-MC ameliorates LF by suppressing inflammatory responses and oxidative stress while preventing the activation of macrophages and HSCs (Figure 9F and G). The dual-responsive nature of these nanocarriers provides enhanced precision in drug delivery by enabling interaction with the physiological environment and intelligently determining the optimal timing and location for drug release. This adaptability underscores the potential of smart nanoparticles as advanced tools for targeted LF therapy.

ROS-Responsive Systems

Excessive accumulation of ROS is a key driver of liver damage and fibrosis progression in LF.[83] Consequently, the development of ROS-responsive smart drug delivery systems has emerged as a promising research focus. Zhang et al designed a multifunctional nano-bioconjugate vesicle, HNP-B-aEV, capable of achieving cellular targeting, ROS scavenging, and inflammation inhibition.[84,85] This system is constructed from cell aggregate-derived extracellular vesicles (aEVs) conjugated with retinol-modified nanoparticles loaded with hydroxychloroquine (HNP) via ROS-sensitive boronic ester linkages (Figure 10).[85] In the high-ROS environment of the liver's Disse space, the boronic ester bonds break responsively, releasing both aEVs and HNP. This dual action not only scavenges ROS but also inhibits HSC activation. Both in vitro and in vivo studies demonstrated that HNP-B-aEV significantly suppresses the release of inflammatory cytokines from M1 macrophages, reshapes the microenvironment, and prevents HSC activation, effectively halting LF progression at its source. Building on this approach, Zhang et al also engineered collagenase-modified nanoparticles co-delivering bardoxolone and siTGF-β to disrupt malignant intercellular crosstalk, reverse the pathological microenvironment, and block TGF-β-driven fibrogenesis.[86] In addition to nano-bioconjugates, injectable hydrogels have gained traction as local delivery systems for liver disease treatment. Yang et al developed a ROS-responsive hydrogel, QCG@Exos$^{miR-4500}$, designed to release exosomes in response to elevated ROS levels.[87] This system integrates

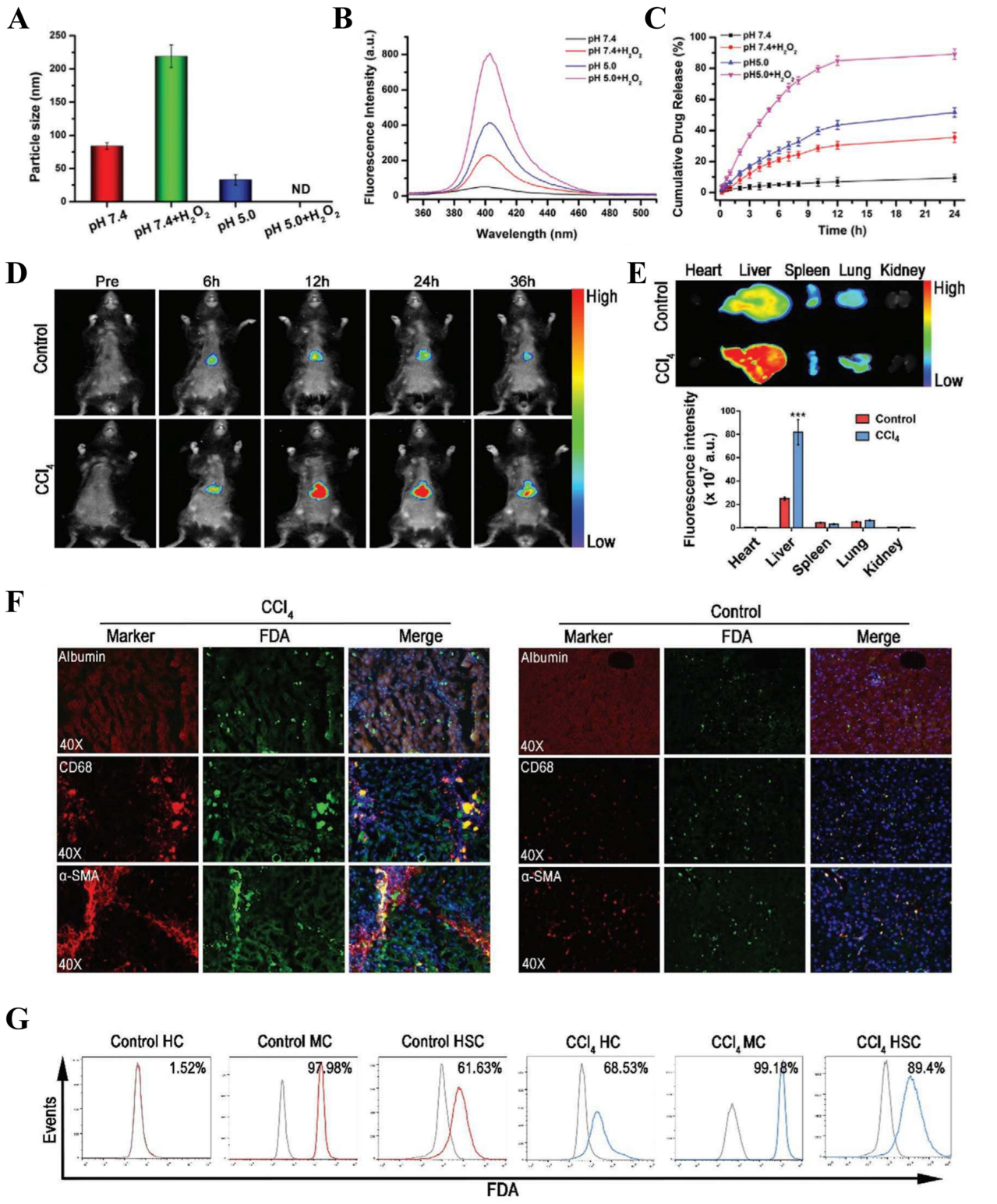

Figure 9 (**A**) Particle size of PD-MC under different conditions (ND indicates not detected). (**B**) Fluorescence intensity of PD after incubation with PD-MC under various conditions. (**C**) In vitro release of PD from PD-MC under different conditions. (**D**) In vivo fluorescence imaging of healthy mice and CCl_4-induced mice after intravenous injection of DiR-loaded nano-micelles (DiR is a fluorescent dye). (**E**) Ex vivo fluorescence imaging of major organs 36 hours after intravenous injection of DiR-labeled nanomicelles. ***$p < 0.001$ versus control healthy mice. (**F**) Distribution of FDA-labeled nano-micelles in liver cells of healthy and CCl_4-induced mice 24 hours post-injection. Immunofluorescence staining of albumin, CD68, and α-SMA indicates the localization of hepatocytes, macrophages, and HSCs, respectively. (**G**) Flow cytometry analysis of cellular uptake and ROS-responsive drug release in isolated primary hepatocytes, macrophages, and HSCs from the livers of healthy and CCl_4-induced mice (HC, hepatocytes; MC, macrophages). Reproduced from Lin L, Gong H-Y, Li R, et al. Nanodrug with ROS and pH Dual-Sensitivity Ameliorates Liver Fibrosis via Multicellular Regulation. Advanced Science. 2020;7(7):1. http://creativecommons.org/licenses/by-nc-nd/4.0/.[82]

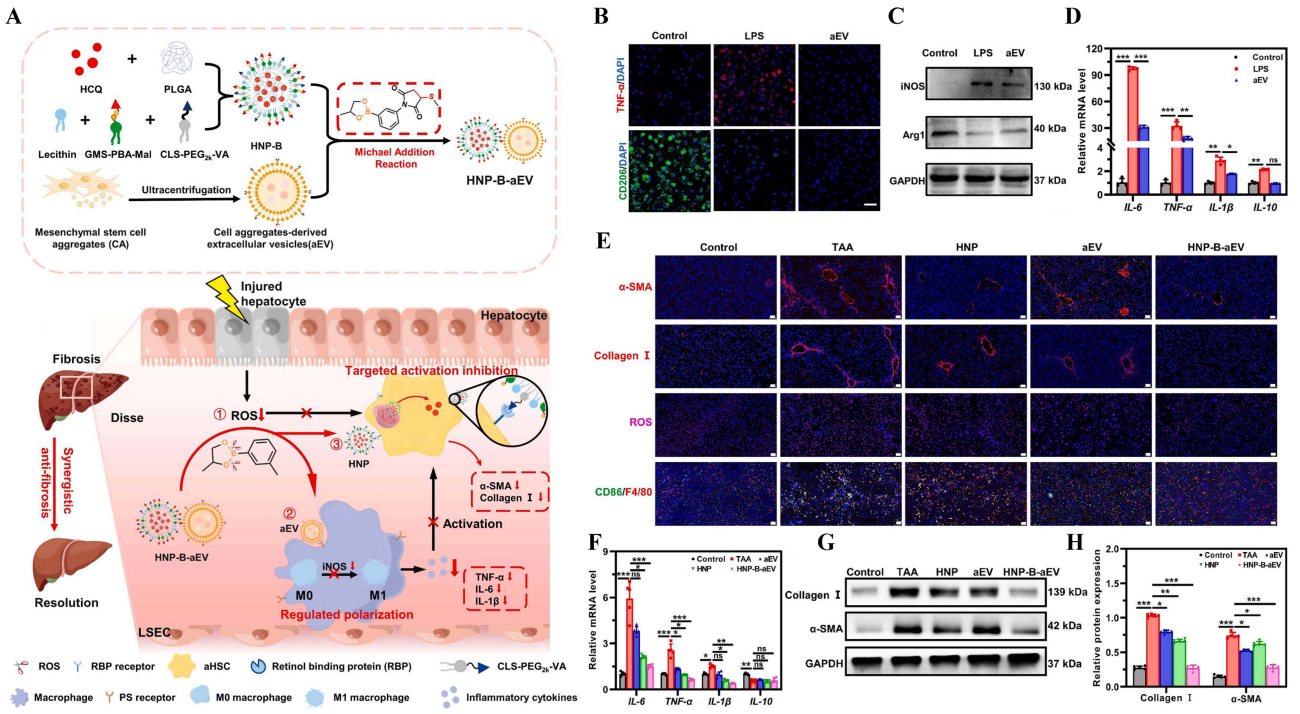

Figure 10 (**A**) Schematic illustration of the preparation process and antifibrotic mechanism of the HNP-B-aEV nano-bioconjugate system. (**B**) Fluorescence microscopy images illustrating macrophage phenotypic shifts following each treatment. Scale bar = 50 μm. (**C**) Western blotting of macrophage lysates to detect changes in phenotype-associated marker proteins. (**D**) Quantitative RT-PCR analysis of pro-inflammatory (eg, TNF-α, IL-6) and anti-inflammatory (eg, IL-10, IL-1β) cytokine transcripts in treated macrophages. To evaluate anti-fibrotic and immunomodulatory activities in vivo, we used a thioacetamide (TAA)-induced model of hepatic fibrosis in mice: (**E**) Confocal laser scanning micrographs of liver sections stained for α-SMA, collagen I, ROS, CD86 (M1 marker), and F4/80 (macrophage marker). Scale bar = 100 μm. (**F**) Relative hepatic mRNA levels of IL-6, TNF-α, IL-1β, and IL-10 determined by qRT-PCR. (**G**) Western blot detection of α-SMA and collagen I proteins in liver tissue. (**H**) Densitometric quantification of α-SMA and collagen I bands normalized to GAPDH. Data were expressed as mean ± SD, n = 5. No significant difference (ns, $P > 0.05$), *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Reprinted from Journal of Controlled Release, 15, Xing J-H, Hou L-S, Zhang K, et al. Microenvironment-responsive nano-bioconjugated vesicles for the multi-pronged treatment of liver fibrosis, 52-66, Copyright 2024, with permission from Elsevier.[85]

reversible boronic ester linkages into gelatin-modified hydrogels through dynamic crosslinking of quaternized chitosan (QCS) and 4-carboxyphenylboronic acid (CPBA). The QCS-CPBA-Gelatin (QCG) hydrogel removes excess ROS from the local microenvironment while releasing $Exos^{miR-4500}$ via the dissociation of boronic ester bonds. This mechanism not only creates a favorable microenvironment for antifibrotic action but also provides an in situ sustained-release drug delivery platform. The ROS - responsive motifs in the aforementioned research primarily rely on boronic ester bonds, which are sensitive to high ROS levels. These dynamic covalent bonds can be cleaved in oxidative microenvironments, enabling controlled release of therapeutic agents. Moreover, dynamic cross - linking strategies (eg, quaternized chitosan and CPBA in QCG hydrogel) enhance responsiveness by facilitating bond dissociation under oxidative stress. These ROS-responsive systems represent innovative therapeutic strategies for LF, leveraging their ability to interact with the pathological microenvironment, neutralize harmful oxidative stress, and deliver therapeutic agents with precision and efficiency.

Enzyme-Responsive Systems

Abnormal expression of specific enzymes during disease progression indicates their critical roles under pathological conditions.[88] Enzyme-mediated drug delivery systems leverage the biological recognition and catalytic properties of these enzymes to achieve targeted drug release within diseased tissues.[89] Enzymes associated with LF include esterases and fibroblast activation protein (FAP). Esterases are overexpressed at sites of inflammation, enabling localized drug release. FAP is a transmembrane serine protease that is specifically upregulated on activated HSCs during fibrosis, enabling the release of antifibrotic drugs exclusively in fibrotic regions.

Xu et al developed an esterase-responsive carbon quantum dot-dexamethasone (CD-Dex) nanodrug for the treatment of LF.[90] Small-sized carbon quantum dots (CDs) are reported to exhibit ROS-scavenging activity due to structural defects

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and active functional groups.[91] The CD-Dex system specifically releases dexamethasone at inflamed sites, effectively mitigating LF.

Similarly, fibroblast activation protein (FAP), which is overexpressed on the surface of activated HSCs in fibrotic livers, presents an attractive therapeutic target.[92] As a post-proline peptidase, FAP can hydrolyze peptide bonds following proline residues, thereby specifically degrading extracellular matrix components. This enzymatic specificity enables FAP - activated drug delivery systems (eg, liposomes) to selectively release therapeutic agents in the fibrotic microenvironment, thereby minimizing off - target effects. For example, FAP can selectively activate liposomes to release antifibrotic agents, such as melittin, exclusively within fibrotic regions by cleaving the liposomes in the LF microenvironment (Figure 11A). This formulation inactivates FAP-positive HSCs and reduces hydroxyproline levels, a marker of fibrosis, while leaving FAP-negative cells unaffected (Figure 11B).[93]

Enzyme-responsive drug delivery systems demonstrate great potential by capitalizing on the unique enzymatic signatures of fibrotic tissues, enabling precise targeting and enhanced therapeutic efficacy while minimizing off-target effects.

Challenges and Future Perspectives

In recent years, significant progress has been made in the application of nanomedicines for the treatment of LF, particularly in the areas of targeted delivery, controlled drug release, and therapeutic efficacy. Thanks to their excellent targeting capabilities, controlled release properties, and multifunctionality, nanotechnology has enabled efficient drug delivery to the LF region, significantly enhancing drug accumulation in the target area while minimizing side effects in non-targeted tissues. For example, specific ligands (such as CD44, RBPR, etc.) can be modified on the surface of nanocarriers to achieve precise targeting of HSCs, thereby inhibiting their activation and excessive ECM accumulation. Moreover, the high drug-loading capacity and smart responsive features of nanomaterials have driven the development of combination therapies, multi-drug delivery, and integrated diagnostic and therapeutic systems, offering new hope for the reversal of LF.

However, several challenges remain in current research, particularly concerning the biosafety and long-term toxicity of nanomedicines. Further investigation is required to assess potential risks, including immune responses, tissue toxicity, and long-term drug accumulation.[94] Additionally, achieving efficient and precise drug delivery, especially in the complex in vivo environment, and overcoming biological barriers for effective drug targeting, remains a significant technical challenge.[95] Moreover, large-scale production of nanocarriers faces issues such as high manufacturing costs and

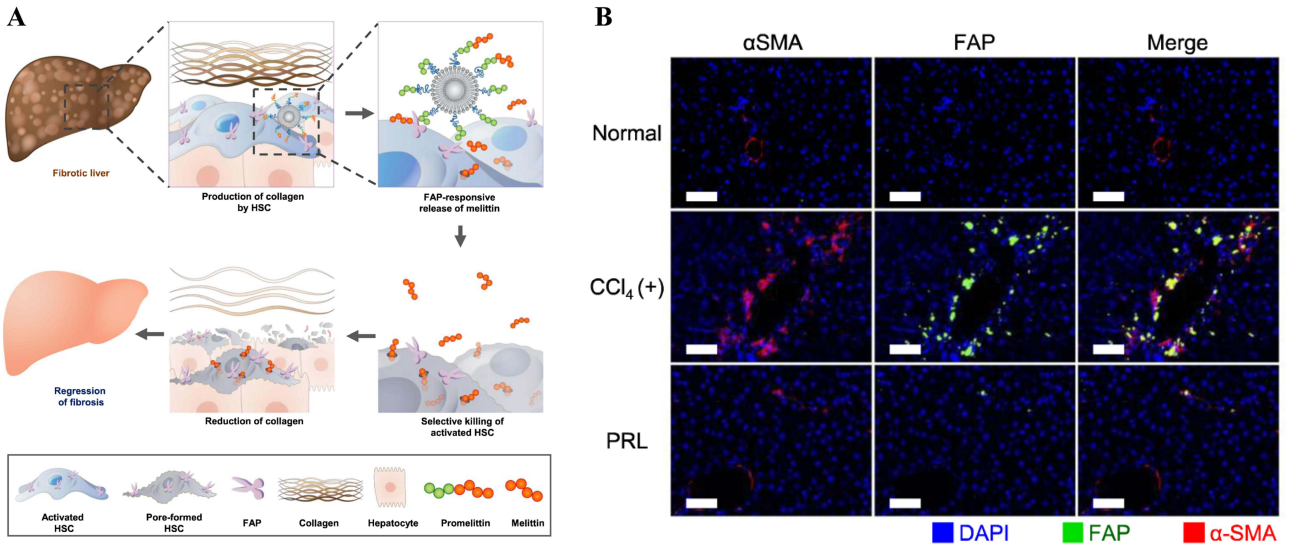

Figure 11 (**A**) Mechanism of the antifibrotic action of melittin-modified liposomes (PRL). (**B**) Immunofluorescence tissue staining of FAP in liver tissues from normal mice and CCl_4-induced LF mice. Scale bar: 50 μm. Reproduced with permission from Lee J, Byun J, Shim G, Oh Y-K. Fibroblast activation protein activated antifibrotic peptide delivery attenuates fibrosis in mouse models of liver fibrosis. Nature Communications. 2022;13(1):1516. http://creativecommons.org/licenses/by/4.0/.[93]

difficulties in batch-to-batch quality control, which limit the successful translation from laboratory research to clinical application.[96] The drug loading efficiency, release rate, and controlled release mechanisms of nanocarriers also need further optimization to ensure stable and controllable therapeutic effects while reducing drug toxicity and side effects.

To address these challenges, future research should focus on the following key areas: optimizing nanocarrier design to enhance targeting and delivery efficiency;[97] exploring multi-target combination therapies, such as integrating nanomedicines, gene therapy, and immunotherapy, to combine different treatment mechanisms for improved efficacy;[98] developing smart responsive nanocarriers for precise drug release and real-time monitoring; and strengthening preclinical studies by utilizing more reliable animal models and multi-center clinical trials to verify safety and efficacy.[99,100] Overcoming these challenges will position nanomedicines as a promising breakthrough for the precise treatment of LF, providing new solutions to improve patient outcomes.

Conclusion

This review aims to summarize the advancements in the application of nanomedicines for the treatment of LF, focusing on the various nanocarriers and therapeutic strategies employed in LF management. Firstly, the review discusses the pathogenesis of LF, providing a detailed analysis of its pathological processes and the current clinical treatment landscape, as well as the major challenges encountered in LF therapy, including drug targeting, bioavailability, and side effects. Next, the review highlights the diverse applications of nanomedicine in LF diagnosis and therapy, including strategies such as passive targeting, active targeting, combination delivery, and smart-responsive drug release. Finally, the article addresses the key challenges faced in the translation of nanomedicines from laboratory research to clinical practice, such as the large-scale production of nanocarriers, controlled release and targeting efficiency, and the assessment of clinical safety. It also proposes potential solutions and outlines future research directions. These discussions provide valuable insights for the clinical application of nanomedicine in LF therapy and contribute to advancing the field of precision medicine.

Data Sharing Statement

Not Applicable. This is a review article, and all relevant information is provided in the article.

Ethical Approval and Consent to Participate

Not Applicable. This is a review paper and do not involve direct research on humans or animals.

Consent for Publication

"Not applicable" as this manuscript does not contain data from any individual person.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All the authors listed meet the criteria for authorship as per the ICMJE guidelines, read the final manuscript and agree to publish this work.

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Disclosure

The authors declare no conflicts of interest in this work.

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