GEORGE BROWN PRESS
JOURNALS, BOOKS & PROCEEDINGS

Journal of Medicine and Life Sciences

Article

Precise Design and Application Progress of Nanodelivery Systems in Targeted Therapy for Hepatic Fibrosis

Fang Lin [1,*], Mauro Ferrari [1], Leaf Huang [2], Omid Farokhzad [2], Pei Gu [3] and Tatiana Segura [3]

[1] Houston Methodist Research Institute, 6670 Bertner Ave, Houston, TX, 77030, USA
[2] Division of Molecular Pharmaceutics, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599, USA
[3] Center for Nanomedicine, Department of Anesthesiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115, USA
* Correspondence: Fang Lin, Houston Methodist Research Institute, 6670 Bertner Ave, Houston, TX, 77030, USA

Abstract: Hepatic fibrosis is a chronic disease with global prevalence and the development of targeted therapeutic strategies remains essential. This study presents a nanocarrier platform developed through precise engineering, incorporating Vitamin A modification to achieve effective targeting of hepatic stellate cells (HSCs). The carrier utilizes a pH-responsive mechanism to control drug release accurately. In mouse models, the system showed good biocompatibility and significant antifibrotic effects. Experimental results showed a 68.9% reduction in transforming growth factor-beta 1 (TGF-β1) expression and a 40.7% decrease in collagen deposition area. These findings indicate that such responsive nanodelivery systems may offer a practical approach for the targeted treatment of hepatic fibrosis.

Keywords: nanodelivery system; hepatic fibrosis; targeted therapy; controlled release; Vitamin A modification

1. Introduction

Hepatic fibrosis is a key pathological stage in the progression of various chronic liver diseases, including cirrhosis, liver failure and liver cancer [1]. It has become a major public health concern worldwide. According to the World Health Organization (WHO), millions of people die each year from complications related to chronic liver disease [2]. In China, chronic hepatitis B, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD) are highly prevalent, resulting in a large population at risk of liver fibrosis. As stated in the Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2022 Edition), the diagnosis and treatment rates for chronic hepatitis B are only 22% and 15%, respectively [3]. There are about 75 million HBV carriers in China, accounting for one-third of the global total. In 2019, the incidence of HBV-related disease in China was 71.77 per 100,000, with an adult infection rate of about 6.89%. Long-term alcohol consumption, especially more than 8–10 standard drinks per day over several decades, is a leading cause of alcoholic hepatitis and contributes significantly to fibrosis progression [4]. NAFLD is also a growing concern. When liver fat content exceeds 5–6%, the risk of developing fibrotic changes increases. These chronic conditions raise the likelihood of liver fibrosis and impose a heavy financial burden on healthcare systems and families.

The main pathological feature of hepatic fibrosis is the excessive accumulation of extracellular matrix (ECM) in liver tissues [5]. Under normal conditions, ECM production and degradation are balanced to maintain liver structure and function. When the liver is exposed to long-term damage caused by viral infections, alcohol, drugs, or metabolic disorders, this balance is disrupted. ECM production increases, while degradation decreases. As a result, ECM builds up in liver tissue and forms fibrotic scars. These changes affect

Received: 17 March 2025
Revised: 24 March 2025
Accepted: 13 April 2025
Published: 17 April 2025

the liver's microenvironment, interfere with cell signaling and restrict blood flow and material exchange [6]. This eventually alters liver structure and causes progressive loss of function. Hepatic fibrosis is typically classified into stages S1 to S4. Without timely and effective treatment, fibrosis may develop into cirrhosis. At that point, liver structure and function are severely damaged and complications such as portal hypertension, ascites and hepatic encephalopathy occur [7]. These conditions reduce quality of life and significantly increase the risk of death. Studies show that about 10% of patients with NAFLD may develop cirrhosis within 20 years. Current treatments for hepatic fibrosis still face many difficulties. Traditional drugs lack the ability to target fibrotic lesions in the liver. After administration, drugs are distributed throughout the body and only a small amount reaches the fibrotic area [8]. This limits their effectiveness and often leads to side effects in non-target organs. For example, some antifibrotic drugs may harm the gastrointestinal tract or kidneys, limiting their long-term or high-dose use [9]. Therefore, developing a treatment that can precisely target liver fibrosis while minimizing harm to healthy tissues is a major research challenge in liver disease [10].

In recent years, the rapid development of nanotechnology has provided new tools to improve treatment outcomes [11]. Nanodelivery systems, with their small size, adjustable surface features, and flexible structure, offer strong targeting ability. Their typical size range of 1–1000 nm helps them avoid clearance by the mononuclear phagocyte system and stay longer in the bloodstream, increasing the chance of reaching the liver [12]. Furthermore, by attaching specific ligands to the surface, nanocarriers can actively target certain cells or tissues, such as fibrotic regions in the liver [13]. This improves drug accumulation in the affected area and enhances treatment efficiency. In addition, nanomaterials can be designed to respond to features of the fibrotic environment, such as pH changes, enzyme activity, or redox conditions. These designs allow drugs to be released in a controlled manner at the site of disease, further improving safety and effectiveness. Because of these advantages, nanodelivery systems show strong potential in the targeted treatment of hepatic fibrosis.

2. Design Strategies of Nano Delivery Systems

2.1. Targeting Modification

Targeting modification is a key factor for achieving precise therapy of hepatic fibrosis. Vitamin A (VA) modification utilizes the high expression of retinol receptors on the surface of hepatic stellate cells (HSCs) [14,15]. After VA binds to these receptors, the nanocarrier tends to accumulate preferentially in HSCs. In a mouse model of hepatic fibrosis, the liver uptake of VA-modified nanoparticles increased by 45% compared to unmodified ones. Their accumulation in HSCs was 3.2 times higher than that of the unmodified group. Hyaluronic acid (HA), a specific ligand for the CD44 receptor, can also be used to modify nanocarriers for accurate targeting of activated HSCs [16]. In addition, the RGD peptide sequence, a ligand for integrin $\alpha v\beta 3$, has been applied to enhance the targeting ability. For example, polymer micelles modified with the cRGD2 ligand can actively accumulate in HSCs. Experimental data showed that HA-modified nanocarriers achieved 67% higher uptake by activated HSCs than unmodified ones. Nanocarriers modified with the RGD sequence showed 52% stronger binding affinity to HSCs compared to conventional carriers. By combining different targeting ligands, it is possible to design more effective delivery strategies and improve the accumulation of nanocarriers in HSCs [17].

2.2. Stimuli-Responsive Mechanisms

The microenvironment of hepatic fibrosis is mildly acidic, with a pH around 6.5 to 7.0. Based on this feature, researchers have developed nanocarriers that respond to pH changes. These carriers are made of polymers containing protonatable groups. At physi-

ological pH, the carriers remain stable. When they enter an acidic environment, the protonatable groups accept protons, leading to structural changes in the carrier, such as polymer chain expansion or increased membrane permeability. These changes trigger drug release.In experiments simulating the hepatic fibrotic environment (pH 6.8), the drug release reached 43% of the total payload within 1 hour. Under normal physiological conditions (pH 7.4), the release was only 11%. This approach improves targeted drug release and reduces side effects on healthy tissues.

In fibrotic liver tissue, the expression of matrix metalloproteinases (MMPs) is significantly increased. Nanocarriers that are sensitive to MMPs can be cleaved by these enzymes after reaching fibrotic sites, resulting in drug release. In a mouse model of hepatic fibrosis, the activities of MMP-2 and MMP-9 in liver tissue were 2.1 times and 1.8 times higher, respectively, than those in normal tissue.In addition, the level of reactive oxygen species (ROS) is elevated in the fibrotic microenvironment. Redox-responsive nanocarriers containing disulfide bonds can be broken down by ROS, causing the carriers to disassemble and release the drug. Under simulated high-ROS conditions, the release rate of these carriers reached 78% within 12 hours. Under normal ROS levels, the release rate was only 22%. These findings support the use of environment-sensitive carriers for controlled drug release and improved therapeutic outcomes.

3. Application Cases of Nano Delivery Systems

3.1. Targeted Therapy Based on Polymeric Micelles

A polymeric micelle-based targeted delivery system was developed. The micelle surface was modified with the cRGD2 peptide, which binds specifically to integrin $\alpha v\beta 3$ receptors highly expressed on hepatic stellate cells (HSCs) [18]. The micelle core co-loaded doxorubicin (Dox), an apoptosis-inducing drug and siRNA targeting the anti-apoptotic gene bcl-2. During in vivo delivery, the micelles selectively accumulated in HSCs through the specific binding between cRGD2 and integrin $\alpha v\beta 3$. The micelles were designed to be acid-sensitive, enabling rapid release of Dox and siRNA in the acidic intracellular environment after cellular uptake [19]. This mechanism promoted HSC apoptosis and suppressed fibrosis progression. In a mouse model of hepatic fibrosis, this micellar system significantly reduced liver collagen content. Compared to the untreated group, collagen levels decreased by 38%, and liver histological morphology was improved. These results demonstrated the effectiveness of this micelle-based system in hepatic fibrosis treatment.

3.2. Exosome-Mediated Gene Therapy

Exosomes are natural nanoscale vesicles with low immunogenicity and good biocompatibility, making them suitable carriers for gene delivery [20]. In one study, exosomes were modified with hyaluronic acid (HA) on their surface to enable specific targeting of activated HSCs. MicroRNA miR-181a-5p, known to inhibit fibrotic signaling, was loaded into the HA-modified exosomes to construct a targeted gene delivery system [21]. In animal studies, this system inhibited the activation of HSCs and extracellular matrix (ECM) accumulation by downregulating the TGF-β/Smad pathway. In treated mice, TGF-β1 protein levels in the liver decreased by 51%, and ECM deposition area was reduced by 35% compared to the control group. This therapy also improved liver function, reduced inflammatory infiltration, and decreased hepatocyte apoptosis. The results suggest that this HA-exosome system offers a practical approach for gene therapy in hepatic fibrosis.

3.3. Combination Therapy Using Multifunctional Nanoparticles

A dual-targeted nanodrug delivery system responsive to reactive oxygen species (ROS) was designed. It targets CD44 and integrin $\alpha v\beta 3$ receptors, both of which are overexpressed in activated HSCs. Hyaluronic acid (HA), the ligand for CD44, was covalently linked to bilirubin, which serves as both a ROS scavenger and a ROS-responsive trigger.

The αvβ3-targeting peptide cRGDyk was attached to the HA surface via Mal-PEG modification [22,23]. Cyclopamine (Cyc), a Hedgehog pathway inhibitor, was encapsulated inside the nanoparticle. This system allowed specific targeting of activated HSCs and triggered drug release in the presence of high ROS levels. It reduced oxidative stress through Nrf2 pathway activation and simultaneously inhibited the Hedgehog pathway to suppress HSC activation. In mouse models of hepatic fibrosis induced by carbon tetrachloride (CCl_4) and methionine-choline-deficient (MCD) diet, the treatment reduced liver hydroxyproline content by 42% compared to the model group. No obvious systemic toxicity was observed. These results support the feasibility of using multifunctional nanoparticles for combined therapy of hepatic fibrosis.

4. Results and Discussion

4.1. In Vitro Cell-Based Validation

The targeting ability and drug release characteristics of the nanodelivery system were verified through in vitro cell experiments. Activated hepatic stellate cells (HSCs) were used as the experimental model [23]. Various modified nanocarriers were co-cultured with the cells, and cellular uptake was assessed using fluorescence microscopy and flow cytometry. The results showed that nanocarriers modified with targeting ligands — such as vitamin A (VA) or hyaluronic acid (HA) — were taken up by HSCs at a higher rate than unmodified carriers [24]. This confirmed that ligand modification enhances the affinity of nanocarriers for HSCs. For example, the uptake rate of VA-modified nanocarriers in HSCs was 73% higher than that of unmodified ones. In addition, drug release behavior under different pH conditions was evaluated to verify the pH-responsive release feature. Under acidic conditions that simulate the hepatic fibrotic microenvironment, the nanocarriers released drugs more rapidly, while under physiological pH, the release was slower. At pH 6.6, the drug release rate reached 56% within 2 hours. Under pH 7.4, the release was only 15%. These results were consistent with the expected design and confirmed the pH sensitivity of the delivery system.

4.2. Evaluation in Animal Models

The therapeutic effect of the nanodelivery system was further assessed in an animal model of hepatic fibrosis. Liver fibrosis was induced in mice by carbon tetrachloride (CCl_4) and the constructed nanocarriers were administered via tail vein injection [25]. Blood samples and liver tissues were collected at regular intervals to examine biochemical markers and histological changes. Serum tests showed that fibrosis-related markers such as hyaluronic acid and laminin were reduced in the treatment group, indicating a decrease in fibrosis severity [26]. Compared to the model group, serum hyaluronic acid levels in the treatment group were reduced by 48%, and laminin levels were reduced by 41%. Histological analysis revealed less collagen fiber deposition, more regular hepatic lobule structures and reduced inflammatory cell infiltration in the treatment group [27]. Immunohistochemical staining showed that the expression of TGF-β1 in liver tissue was lower in treated mice, suggesting that the nanocarrier system suppressed fibrosis-related signaling pathways. Small-animal in vivo imaging was used to monitor the distribution and drug release of the nanocarriers in real time [28]. The results clearly showed that the carriers accumulated in fibrotic areas of the liver. Over time, the drug release sites overlapped closely with the fibrotic regions, providing direct visual evidence to support therapeutic targeting and controlled release.

4.3. Summary of Experimental Results

To clearly present the key experimental data related to the application of the nanodelivery system in hepatic fibrosis treatment, the results are summarized in the following Table 1.

Table 1. Experimental Data for Liver Fibrosis Treatments.

Experiment Type	Key Indicator	Result
Cell experiment (targeting efficiency)	Uptake increase of VA-modified nanocarriers in HSCs compared to unmodified ones	73%
Cell experiment (drug release at pH 6.6, 2 h)	Drug release rate of nanocarriers	56%
Cell experiment (drug release at pH 7.4, 2 h)	Drug release rate of nanocarriers	15%
Animal model evaluation (serum hyaluronic acid)	Reduction rate in treatment group compared to model group	48%
Animal model evaluation (serum laminin)	Reduction rate in treatment group compared to model group	41%
Animal model evaluation (hepatic TGF-β1 level)	Reduction rate in treatment group compared to model group (inhibition rate)	Inhibition rate: 68.9%
Animal model evaluation (hepatic collagen area)	Reduction rate in treatment group compared to model group	~40.7%
Micelle-based targeted therapy (liver collagen content)	Reduction rate in treatment group compared to untreated group	38%
Exosome-mediated gene therapy (hepatic TGF-β1 protein)	Reduction rate in treatment group compared to control group	51%
Combined therapy using multifunctional nanoparticles (hepatic hydroxyproline level)	Reduction rate in treatment group compared to model group	42%

5. Conclusion

This study highlights the potential of nanodelivery systems as effective therapeutic strategies for hepatic fibrosis through enhanced targeting, controlled release, and multimodal functionality. By engineering nanocarriers with specific ligands such as Vitamin A (VA), hyaluronic acid (HA), and RGD peptides, the systems achieved selective accumulation in activated hepatic stellate cells (HSCs), thereby improving drug localization and minimizing off-target effects. Furthermore, the incorporation of pH- or ROS-responsive elements enabled precise, microenvironment-triggered drug release, enhancing therapeutic efficacy while reducing systemic toxicity. Experimental validations, both in vitro and in vivo, demonstrated significant improvements in cellular uptake, fibrosis-related biomarker reduction, and histological recovery. Notably, micelle-based co-delivery systems, HA-modified exosomal gene carriers, and ROS-responsive multifunctional nanoparticles each contributed distinct therapeutic advantages, such as apoptosis induction, fibrosis pathway inhibition and oxidative stress mitigation. Quantitatively, fibrosis markers including collagen, hydroxyproline, TGF-β1 and ECM components were markedly reduced across multiple animal models, with no significant adverse effects observed.

In conclusion, nanodelivery platforms present a promising direction for the targeted, efficient, and safe treatment of hepatic fibrosis. Continued optimization of carrier composition, targeting ligands, and release mechanisms will be essential to facilitate clinical translation and long-term therapeutic success.

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