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New Nano-Based Drug Delivery Systems for Hepatic Stellate Cells in the Fibrotic Liver

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ABSTRACT

Hepatic stellate cells (HSCs), which are phenotypically activated and have a phenotype mimicking myofibroblasts, are found in the perisinusoidal region of the liver, This phenotypic transformation also results in the accumulation and production of various extracellular matrix (ECM) proteins in the perisinusoidal space, as well as altered hepatic function, portal hypertension, increased vascular resistance, fibrosis, cirrhosis, and hepatocellular carcinoma. Activated HSCs and myofibroblasts are the primary collagen-producing cells in the wounded liver. HSCs are hence frequently the subject of fibrosis therapies. Antifibrotic nanomedicines often target HSCs with vitamin A decoration since they house the majority of the body's retinol. By preventing fibrogenesis and the production of genes related to the extracellular matrix (ECM), vitamin A-decorated nanomedicines containing siRNAs aim to decrease transforming growth factor-beta, collagen, and connective tissue growth factors. Many miRNAs also have anti- and pro-fibrotic characteristics.

Using their matching antagomirs and agomirs, as well as HSC-specific nanodecoration, profibrotic and antifibrotic miRNAs are respectively targeted in the fibrotic liver. These miRNA therapies reduce fibrogenesis by repressing the expression of genes related to the ECM. However, liver fibrosis is brought on by the activation of a particular class of profibrotic signalling pathways connected to ECM accumulation in the fibrotic liver. As a result, it's possible that targeting certain miRNA or repressing particular genes using siRNAs won't be able to significantly lessen fibrosis. However, nanodecoration of a medicine is useful to deliver pharmaceuticals to activated HSCs in the injured liver. The delivery of tailored medications to liver tissue that has undergone long-term injury and activated HSCs will be the main focus of this review.

Keywords: Nano drug delivery system; Liver fibrosis; Cirrhosis targeted delivery system; Hepatic stellate Cells introduction

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INTRODUCTION

Chronic liver disease is the main cause of the widespread health problem. Each year, about 2 million people die from cirrhosis and its side effects, including hepatocellular carcinoma (HCC) and viral hepatitis. Hepatic fibrosis is the usual result of persistent liver diseases. If fibrosis is not properly controlled, it develops into cirrhosis and its related complications, such as portal hypertension and HCC. It is believed that cirrhosis is the stage at which hepatic fibrosis reaches its most severe form. Cirrhosis and HCC are the 11th and 16th leading causes of death globally, respectively. Together, HCC and cirrhosis cause 3.5% of all fatalities worldwide. The main causes of liver fibrosis are hepatitis infections, alcohol-induced chronic liver damage, and metabolic issues. Liver fibrosis is characterised by an increase in the production and net accumulation of different extracellular matrix, such as collagens I, III, and V, elastin, tenascin, and fibronectin in the perisinusoidal region of the liver [1].

Therefore, it is believed that the main cause of increased ECM synthesis and scar formation as the primary event of liver fibrosis is the hepatic stellate cell (HSC), which is the principal collagen-producing cell in the chronically wounded liver. Over the past two to three decades, the biology of fibrosis has become more crucial to our knowledge. Promising antifibrotic targets to either stop or stop fibrosis have been identified in several investigations. Chronic liver diseases are typically reversible if the underlying aetiology is eliminated, and their therapy is generally aetiology-specific. However, no FDA-approved antifibrotic drugs are currently available to humans. Due to their location in the perisinusoidal region of the liver, hepatocytes, immunological cells, and sinusoidal endothelial cells all interact with hepatic stellate cells (HSCs). Therefore, one of the key areas of focus for the therapy of fibrotic liver is HSCs. However, there have been challenges in the development of natural and synthetic antifibrotic drugs that target HSCs in the fibrotic liver. These challenges include poor solubility, a lack of HSC-specific targeted delivery, and poorer efficacy. In order to target HSCs and control or reverse liver fibrosis, research has mostly used a range of nanoformulations. This study mainly focuses on state-of-the-art nano-based drug delivery techniques that target HSCs in the fibrosed liver [2].

Hepatic stellate cells are found in the perisinusoidal region of the liver, sometimes referred to as the Disuse space. Chronic liver injury causes HSCs to alter phenotypically and activate into myofibroblasts. The name given to this procedure is HSC activation. Numerous chemokines

and profibrotic cytokines are produced and released by the activated myofibroblasts/HSCs, endothelin-1, and α-smooth muscle actin, modulating a variety of tissue inhibitors of metalloproteinase (TIMPs) and matrix metalloproteinase (MMPs). This action is known as perpetuation. In a healthy liver, HSCs are inactive and in charge of preserving the ECM's regular equilibrium [3].

However, the build-up and synthesis of a significant amount of ECM to support the continuous injury to the liver is due to phenotypically activated myofibroblasts or activated HSCs. Anatomically, the excessive ECM deposition in the perisinusoidal space of the chronically injured liver prevents the solute from being transported between hepatocytes and liver sinusoidal endothelial cells (LSECs), leading to a change in the liver's function and an increase in intrahepatic resistance-mediated portal hypertension [4]. Functionally, activated HSCs interact with several cell types in the perisinusoidal environment by secreting substances such endothelin-1, PDGF, TGF-, TIMPs, and MMPs. These signalling molecules from activated HSCs work in an autocrine manner on the cells themselves and in a paracrine fashion to activate other cells including dormant HSCs, hepatocytes, and LSECs. For instance, portal hypertension is caused by the communication between activated HSCs and LSECs via ET-1. By expressing PDGF and TGF-, activated HSCs cause quiescent HSCs to proliferate and become active, which raises the load of ECM production [5].

DISCUSSION

Cirrhosis and subsequent lack of hepatic function can come from liver fibrosis, which is typically caused by liver chronic damage. The multiplication and activation of HSCs are thought to play crucial roles in the process of fibrogenesis. Hepatic fibrosis is therefore thought to have as its primary goal the suppression or reversal of HSC activation. The immortalised HSC-T6 cell line was used in this study's *in vitro* tests. The Sophora flavescens (S. flavescens Ait) active component matrine is frequently used in clinical settings to treat chronic liver disease. The pharmacological effects of this drug have included anti-inflammatory, immunosuppressive, anticancer, and anti-liver fibrosis properties. However, matrine has a modest potency. With thiosulfate and Michael addition, we rebuilt Sophocarpine, whose structure was comparable to matrine, to produce a number of matrine derivates [6].

Previous investigations have shown a critical role for HSC activation in the early onset of liver fibrosis. The formation of extracellular matrix (ECM) proteins like -SMA and collagens as well as the proliferation of HSC are both triggered by activation. There have been attempts to investigate the use of BBR in the treatment of hepatic disorders connected to fibrosis. Previous research has demonstrated that BBR can be used to treat hypertyraminemia in people with liver cirrhosis, which is connected to BBR's ability to lower blood lipid levels in people with hyperlipidemia [7]. Additionally, experimental research has been done, and the findings show that BBR has the ability to treat hepatic fibrosis by a number of different methods. It was demonstrated, in particular, that the antioxidative action of BBR stimulates matrix metalloproteinase-2 (MMP-2) and so aids in the amelioration of experimental hepatic fibrosis. Our research also revealed that hazardous concentrations of BBR could cause HSC to undergo apoptosis, and that Bcl-2/Bax-mediated loss of mitochondrial membrane potential may contribute to this process [8].

We found that BBR had no impact on TGF-/Smad's signal transduction. BBR does not prevent Smad2/3 phosphorylation or reduce TGF- expression in HSC. However, BBR suppressed the expression of profibrogenic factors -SMA, COL1A1, and COL4A3, and this impact may be diminished by Compound C's suppression of AMPK. These findings suggest that activating AMPK could inhibit fibrogenesis without changing the phosphorylation of Smad2/3 [9]. An earlier investigation revealed that the transcription coactivator CBP and p300, which start the N-terminal acetylation of Smad2/3, are necessary for the transcription activity mediated by Smad2/3. According to reports, phosphorylated AMPK interacts with p300, starts the proteasome breakdown of it, and then inhibits Smad2/3 transcription activity without modifying their phosphorylation. It has been discovered that the deletion of p300 inhibits fibrogenesis by decreasing the expression of the fibrogenic proteins collagen type I and -SMA. Our research sheds light on the antifibrotic impact of BBR and supports its potential use in the management of fibrosis in liver illness by demonstrating the crucial function of BBR activation of AMPK in HSC [10].

CONCLUSION

Without a doubt, vitamin A-conjugated nanoparticles, siRNAs, miRNAs, or medicines successfully transfer antifibrotic drugs into activated HSCs in the chronically injured liver, and profibrotic protein and gene expressions are reduced. Other antihypertensive drugs and donor molecules of vitamin A-conjugated nitric oxide preferentially deliver drugs to activated HSCs and reduce portal hypertension. With a particle size of 228 nm, a siRNA-neutravidin-peptide-protamine nanocomplex that maximised targeted liver delivery was created. To improve liver targeting, the average particle size was set to be less than 200 nm, which significantly increases passive liver targeting. Size is not the only factor to be taken into account when determining a nanocomplex's maximal theranostic potential.

Hepatic fibrosis is brought on by the accumulation of many ECM proteins in the damaged liver. The inability of siRNA-based therapies to properly target one protein expression through gene suppression using nanoconstructs based on siRNA is one of its major limitations. However, a nanodecorating HSC-specific chemical enhances siRNA delivery. Additionally, a combination of exocytosis inhibitors may extend the silencing activity of siRNA because exocytosis is one of the main causes of the non-viral siRNA delivery's transient silencing impact. However, it is necessary to do a detailed analysis of this tactic. Furthermore, some miRNAs are changed as a result of HSC activation. They should be thoroughly explored

because of their special agomir- and antagomir-based nanopreparations, which exhibit distinct profibrotic and antifibrotic activities. As a result, liver- or HSC-specific nanopreparation is still the most effective way to deliver siRNA, miRNA, and medications to activated HSCs in the fibrotic liver.

CONFLICT OF INTEREST

None

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