Mini Review

It Medical Team
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International Journal of Drug Development and Research
0975-9344

2023
Vol. 15 No. 1: 991

Novel Nano-Based Drug Delivery Systems for Fibrotic Liver's Hepatic Stellate Cells

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Citation: Jain V (2023) Novel Nano-Based Drug Delivery Systems for Fibrotic Liver's Hepatic Stellate Cells. Int J Drug Dev Res J, Vol. 15 No. 1: 991.

Abstract

Hepatic stellate cells (HSCs) are phenotypically active and develop a phenotype resembling myofibroblasts in the perisinusoidal region of the liver. Affected hepatic function, portal hypertension, increased vascular resistance; fibrosis, cirrhosis, and hepatocellular carcinoma are all results of this phenotypic transformation, which is also responsible for the accumulation and production of various extracellular matrix (ECM) proteins in the perisinusoidal space. In the injured liver, the main collagen-producing cells are activated HSCs/myofibroblasts. As a result, HSCs are frequently the focus of fibrosis treatments. Since HSCs contain the majority of the body's retinol, antifibrotic nanomedicine frequently target them with vitamin A decorating. Transforming growth factor-beta, collagen, and connective tissue growth factors are targeted by vitamin A-decorated nanomedicine with siRNAs to reduce fibrosis by inhibiting fibrogenesis and the expression of genes linked with the extracellular matrix (ECM).

Numerous miRNAs also have pro- and antifibrotic properties. Profibrotic and antifibrotic miRNAs are targeted in the fibrotic liver using their corresponding antagomirs and agomirs, respectively, together with HSC-specific Nano decoration. By inhibiting the expression of genes linked to the ECM, these miRNA therapies lower fibrogenesis. However, the activation of a distinct class of profibrotic signalling pathways linked to ECM build-up in the fibrotic liver is what causes liver fibrosis. Therefore, suppressing individual genes with siRNAs or specifically targeting miRNA may not be able to alleviate fibrosis to a higher level. To transport medications to activated HSCs in the wounded liver, however, nanodecorating of a drug is helpful. The focus of this review will be on targeted drug delivery to activated HSCs in the liver that has sustained long-term damage.

Keywords: Drug Delivery; Fibrotic Liver; Nanomedicine; Hepatic stellate cells; Nano-Based; Nanotechnology

Received: 30-Dec-2022, Manuscript No. ijddr-23-13399; **Editor assigned:** 09-Jan-2023, Pre-QC No. ijddr-23-13399(PQ); **Reviewed:** 16-Jan-2023; QC No. ijddr-23-13399; **Revised:** 23-Jan-2023; Manuscript No. ijddr-23-13399(R); **Published:** 30-Jan-2023, **DOI:** 10.36648-0975-9344-15.1-991

Introduction

The primary factor causing the widespread health issue is chronic liver disease. Cirrhosis and its consequences, including hepatocellular carcinoma (HCC) and viral hepatitis, are responsible for over 2 million deaths each year. The typical outcome of chronic liver disorders is hepatic fibrosis. Fibrosis advances into cirrhosis and its associated consequences, such as portal hypertension and HCC, if it is not effectively managed. Hepatic fibrosis is thought to progress to its most advanced form at cirrhosis. In terms of deaths worldwide, cirrhosis and HCC are ranked 11th and 16th, respectively. HCC and cirrhosis account for 3.5% of global fatalities collectively. Hepatitis infections, chronic liver damage brought on by alcoholic consumption, and metabolic problems are the main causes of liver fibrosis [1].

The increased synthesis and net accumulation of various extracellular matrixes, including collagens I, III, and V, elastin, tenascin, and fibronectin in the perisinusoidal area of the liver are the hallmarks of liver fibrosis. The hepatic stellate cell (HSC), which is the main collagen-producing cell in the chronically injured liver, is therefore thought to be the mediator of enhanced ECM synthesis and scar formation as the primary event of liver fibrosis. Our understanding of the biology of fibrosis has been

more important over the past two to three decades. Several studies have revealed promising antifibrotic targets to either prevent or reverse fibrosis. After the underlying aetiology is removed, chronic liver illnesses are frequently reversible, and their treatment is primarily etiology-specific [2].

Hepatocytes, immune cells, and sinusoidal endothelial cells are all in communication with the hepatic stellate cells (HSCs) because of their placement in the per sinusoidal region of the liver. HSCs are thus one of the main targets for the treatment of fibrotic liver. But there have been difficulties in the development of natural and synthetic antifibrotic medications that target HSCs in the fibrotic liver, including poor solubility, a lack of HSC-specific targeted delivery, and lower efficacy. As a result, research has mostly used a variety of nanoformulations to target HSCs and regulate or reverse liver fibrosis. The main focus of this review is on cutting-edge nano-based drug delivery methods that target HSCs in the fibrosed liver [3].

The majority of chronic liver injuries, such as those brought on by alcohol, chronic viral hepatitis, autoimmune, parasite, and metabolic illnesses, as well as less frequently occurring toxic or drug exposure, culminate in fibrosis, an incorrect tissue repair of the liver. If fibrosis is left untreated, it can turn into cirrhosis. Contrary to conventional wisdom, which holds that cirrhosis is an uncurable condition, there is strong evidence that even cirrhosis may be treatable. With high morbidity and mortality, liver fibrosis is a significant public health concern. Cirrhosis affects hundreds of millions of individuals globally. The three most frequent causes are nonalcoholic fatty liver disease, alcoholic liver disorders, and chronic viral hepatitis B and C. Hepatic fibrosis-cirrhosis prevalence is anticipated to rise, in part because of the rising rates of obesity and metabolic syndrome, particularly in industrialised nations [4].

Liver fibrosis has a complicated pathogenesis that differs depending on the type of hepatic injury. Parenchymal cells often regenerate and replace necrotic and apoptotic cells after acute liver damage; this process is accompanied by an inflammatory response and a limited deposition of extracellular matrix (ECM). When the damage is left untreated, the regenerative process eventually fails, and the hepatocytes are replaced by an abundance of extracellular matrix (ECM) that is primarily made up of collagen type's I–III–IV, fibronectin, elastin, laminin, and proteoglycans. The primary sources of ECM are hepatic stellate cells (HSC) [5].

There is no established cure for liver fibrosis, although it is recognised that preventing liver damage events, such as quitting drinking or successfully treating viral hepatitis, helps to regulate the condition. But in the vast majority of patients, these measures don't seem to be enough to stop the progression to cirrhosis. Even though there have been significant improvements in our understanding of the pathophysiology of hepatic fibrosis over the past 20 years, there are still significant gaps in our ability to turn this fundamental knowledge into effective anti-fibrotic medications. The variety of the pathophysiology of liver fibrosis should be considered when developing treatment plans, and all cell types, beginning with HSC and hepatocytes should be targeted [6].

The use of medicinal plants as antifibrotic medicines is becoming more and more common, thanks to their security, affordability, and adaptability. We've already discussed how herbal remedies prevent HSC activation and lessen ECM build-up to lessen liver fibrosis. The manipulation of certain cell lines' apoptosis, among other antifibrotic processes, might be able to account for this activity. The induction of HSC apoptosis and the protection of hepatocytes from apoptosis are the two additional mechanisms by which the bioactive compounds from twelve known hepatoprotective plants, such as Curcuma longa, Silybum marianum, Ginkgo biloba, Salvia miltiorrhiza, Glycyrrhiza glabra, Scutellaria baicalensis, Bupleurum falcatum [7].

Discussion

The primary factor contributing to liver fibrosis and hepatic damage is the abnormal activation of HSCs and subsequent persistent collagen fibre deposition. We created a liver fibrosis rat model using DEN, the chemical that is most frequently utilised to cause liver fibrosis in rats. HSC-T6 was created from SD rat hepatic stellate cells that had the SV40 antigen transfected into them, so it had both the properties of dormant HSC and the capacity for proliferation and activation of myofibroblasts. We chose HSC-T6 as the in vitro liver fibrosis model because these cells could express -SMA and extracellular matrix. Fibrosis in the liver is a challenging pathological condition [8].

Transforming growth factor (TGF), platelet-derived growth factors B and D (PDGF-B and PDGF-D), endothelin-1, and tumour necrosis factor (TNF) - are just a few of the cytokines and growth factors that are involved in fibrogenesis. The major fibrogenic cytokine was discovered to be TGF-. TGF- may cause collagen deposition by activating HSCs to MFBs, accelerating matrix gene expression, reducing matrix breakdown, and upsetting homeostasis. Activation of HSC can also encourage TGF-secretion, creating a positive feedback loop that speeds up liver fibrosis. Therefore, we decided to use TGF- to in vitro mimic liver fibrosis [9].

TGF-/Smads are thought to be a key factor in liver fibrosis since they primarily promote it by activating the downstream Smad signalling pathway. TGF- induces Smad7, an inhibitory factor that controls fibrogenic signalling to stop excessive ECM deposition. As a result, the low expression of Smad7 in liver fibrosis may aid in the advancement of hepatic fibrosis. Smad7 cannot be activated through the pSmad3L pathway in chronic liver damage, leading to constitutive fibrogenesis in MFBs. Additionally, prior research has demonstrated that epigenetic alterations, including as microRNAs, histone modifications, promoter hypermethylation, and Smad phospho-isoforms associated with Smad7 expression, cause the decrease of Smad7 expression. The 3'UTR region of Smad7 can be targeted by miR-195, according to a microRNA target prediction analysis [10].

So, the purpose of our research was to find out if miR-195 influenced Smad7 expression and HSC activation. Our research demonstrated that in vivo, liver fibrotic tissues had higher levels of miR-195 expression than control tissues. The findings suggested that TGF- may increase miR-195 transcription and drive HSC activation and proliferation. In line with prior studies, we discovered that TGF- enhanced Smad7 mRNA expression at

24 h but decreased Smad7 protein expression at 24 h, followed by a reduction in Smad7 mRNA expression at 48 h and 72 h. According to Yoshida and Matsuzaki, acute liver injury to rats caused a temporary increase in Smad7, which was followed by a decrease with chronic liver injury [11].

Additionally, by conducting dual luciferase reporter assays, we evaluated this theory. The human wild type and mutant Smad7 3'UTR target sequences were annealed into oligonucleotides, which were then cloned into the pMIR-Report Luciferase plasmid. We used HEK 293T cells since our preliminary research indicated that transfected HSC-T6 had low relative luciferase activity. The outcomes demonstrated that miR-195 targeted Smad7, and that miR-195 bound specifically to the 3'UTR region of Smad7 mRNA. MiRNAs have the potential to be used as a new fibrosis biomarker, according to earlier investigations. However, due to the difficulty in obtaining liver tissue samples, our upcoming research will focus on the precise function of serum/plasma miR-195 in controlling HSC activation and liver fibrosis [12].

Conclusion

Without a doubt, antifibrotic pharmaceuticals are successfully delivered into activated HSCs in the chronically wounded liver by vitamin A-conjugated nanoparticles, siRNAs, miRNAs, or medications, and profibrotic protein and gene expressions are decreased. Other antihypertensive medications and vitamin A-conjugated nitric oxide donor molecules specifically transport medications to activated HSCs and lower portal hypertension. The average particle size was set to be less than 200 nm in order to improve liver targeting, which considerably encourages passive liver targeting. For a nanocomplex to have the highest theranostic potential, size is not the sole consideration. The build-up of many ECM proteins in the injured liver results in hepatic fibrosis.

One of the key drawbacks of siRNA-based therapies is that they cannot effectively target one protein expression through gene silencing utilising nanoconstructs based on siRNA. However, siRNA delivery is improved by nanodecorating HSC-specific compounds. Additionally, as exocytosis is one of the primary causes of the non-viral siRNA delivery's temporary silencing effect, a combination of exocytosis inhibitors may prolong the silencing activity of siRNA. But soon, this strategy needs to be thoroughly researched. Moreover, during HSC activation, a number of miRNAs are altered. Due to their distinct profibrotic and antifibrotic capabilities, their unique agomir- and antagomir-based nanopreparations should be researched further, respectively. As a result, the gold standard method for delivering siRNA, miRNA, and medicines into activated HSCs in the fibrotic liver is still liver- or HSC-specific nanopreparation.

Conflict of Interest

None

Acknowledgement

None

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