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TOPIC HIGHLIGHT

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Nanotechnology applications for the therapy of liver fibrosis

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Abstract

Chronic liver diseases represent a major global health problem both for their high prevalence worldwide and, in the more advanced stages, for the limited available curative treatment options. In fact, when lesions of different etiologies chronically affect the liver, triggering the fibrogenesis mechanisms, damage has already occurred and the progression of fibrosis will have a major clinical impact entailing severe complications, expensive treatments and death in end-stage liver disease. Despite significant advances in the understanding of the mechanisms of liver fibrinogenesis, the drugs used in liver fibrosis treatment still have a limited therapeutic effect. Many drugs showing potent antifibrotic activities *in vitro* often exhibit only minor effects *in vivo* because insufficient concentrations accumulate around the target cell and adverse effects result as other non-target cells are affected. Hepatic stellate cells play a critical role in liver fibrogenesis , thus they are the target cells of antifibrotic therapy. The application of nanoparticles has emerged as a rapidly evolving area for the safe delivery of various therapeutic agents (including drugs and nucleic acid) in the treatment of various pathologies, including liver disease. In this review, we give an overview of the various nanotechnology approaches used in the treatment of liver fibrosis.

Key words: Liver fibrosis; Nanotechnology; Nanoparticles; Hepatic stellate cells; Antifibrotic drugs, Cirrhosis

Core tip: New drugs or new drug delivery strategies to cure liver fibrosis are needed to find effective therapeutic options for this pathologic condition. Therapies based on nanotechnologies have emerged as an innovative and promising alternative to conventional therapies. This work aims to review the most recent literature about the use of nanotechnology approaches to reduce liver fibrosis.

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INTRODUCTION

Chronic liver diseases (CLD) are disorders that chronically affect the liver, undermining its capacity to regenerate after injury and triggering a wound-healing response that involves a range of cell types and mediators which try to limit the injury and set in motion the fibrogenesis

mechanisms. The sustained signals associated with CLD of whatever origin (infections, drugs, metabolic disorders, autoimmunity, *etc.*) are required for significant fibrosis to accumulate, which predisposes to the development of cirrhosis and its complications.

Liver fibrogenesis in response to a chronic infection associated with hepatitis viruses (HBV and HCV), chronic alcohol consumption, genetic abnormalities, steatohepatitis, autoimmunity, *etc.* is the consequence at the cellular and molecular levels of the activation of hepatic stellate cells (HSCs) and their transformation into myofibroblasts which overproduce extracellular matrix, mainly type Ⅰ and Ⅲ collagens. Liver fibrosis may regress following specific therapeutic interventions, but no anti-fibrotic drugs are currently available in clinical practice other than those which eliminate the risk factors. Indeed, several clinical trials testing potential anti-fibrotic drugs [such as angiotensin Ⅱ antagonists, interferon gamma, peroxisomal proliferator activated receptor (PPAR) gamma ligands, pirfenidone, colchicine, silymarin, polyenylphosphatidylcholine, ursodeoxycholic acid and Interleukin-10], have failed to observe either a halt in the progression of liver fibrosis or its reversal[1].

An important disadvantage of the standard therapy is that it is unable to provide a sufficient concentration of the therapeutic agent to treat liver disease and/or it leads to side effects.

Recently, therapies based on nanotechnologies have emerged as an innovative and promising alternative to conventional therapy. Nanotechnology is a rapidly growing branch of science focused on the development, manipulation and application of materials ranging in size from 10-500 nm either by scaling up from single groups of atoms or by refining or reducing bulk materials into nanoparticles (NPs). Currently, nanoparticles are being constructed with biocompatible materials and they possess great potential in delivering drugs in a more specific manner: either passively by optimizing the physicochemical properties of the drug nanocarriers (such as the size and surface properties) or actively by using tissue/cell-specific homing devices which allow the targeting of the disease site, while minimizing side-effects. Therefore, NPs can be engineered as nanoplatforms for the effective and targeted delivery of drugs, also thanks to their ability to overcome many biological, biophysical, and biomedical barriers.

In recent years, nanomedicine-based approaches have been explored for liver disease treatment. In this review, we will describe the most common NP types employed in the treatment of fibrotic liver diseases.

NANOTECHNOLOGIES IN HUMAN DISEASES

Therapeutic NPs are generally defined as nanostructures constituted by therapeutic drugs, peptides, proteins or nucleic acids loaded in carriers with at least one length in the nanometer range. Drugs and imaging labels which cannot achieve an effective and targeted delivery due to biological, biophysical, and biomedical barriers can be engineered as NPs. The possibility to incorporate drugs and genes into NPs through the conjugation or coating of ligands specifically binding to target cells or tissues opens a new era for delivering drugs and genes selectively to the disease site. There are several advantages to using NP delivery systems: (1) protection of the therapeutic agent, especially nucleic acid, against inactivation until it reaches the site of action; (2) feasibility of incorporation of both hydrophilic and hydrophobic agents; (3) optimization of pharmacological effectiveness (increased bioavailability of drugs); (4) reduction of toxicity and side effects of the drug; (5) reduction of drug blood level fluctuations (lower risk of ineffective or toxic concentration); (6) potential broad spectrum of administration routes (external, ophthalmic, oral and parenteral); (7) controlled drug release; and (8) active targeting due to the possibility of obtaining a greater affinity of the nanoparticle system (functionalized nanoparticle) for certain tissues. Following systemic administration, conventional NPs are opsonized by plasma proteins, recognized as foreign bodies and rapidly captured by the reticuloendothelial system (RES). The liver and the spleen are the major organs of accumulation of NPs[2,3] due to their rich blood supply and the abundance of tissue-resident phagocytic cells, therefore liver targeting by NPs may be favorable for treating liver diseases[2,3].

The uptake and distribution of NPs depend on their size: (1) NPs with a mean diameter > 400 nm are quickly captured by the RES; and (2) NPs with a diameter < 200 nm show prolonged blood circulation and a relatively low rate of RES uptake[4]. On the other hand, to reduce opsonization by blood proteins and to prolong bloodstream circulation by limiting RES uptake and reducing immunogenicity/antigenicity, biologically inert hydrophilic polymers, such as poly(ethylene glycol) (PEG), have been covalently linked to the nanocarrier surface[5,6]. These types of NPs are commonly called "stealth" NPs[5,6].

Nanomedicine is referred to as the field of medicine that deals with the application of nanotechnology to address medical problems[7-9], and recently nanomedicine-based approaches have been explored for liver disease treatment.

COMMON NP TYPES TO BE EMPLOYED FOR THE TREATMENT OF LIVER DISEASE

The variety of materials that can be used to create NPs is enormous and the number of NPs used in biomedical research and drug delivery is rapidly increasing. They can be classified into two major types: inorganic and organic NPs. Here, we briefly summarize only the structure, properties and characteristics of some of the most commonly-used NPs for the treatment of liver fibrosis.

Inorganic NPs have received great attention because

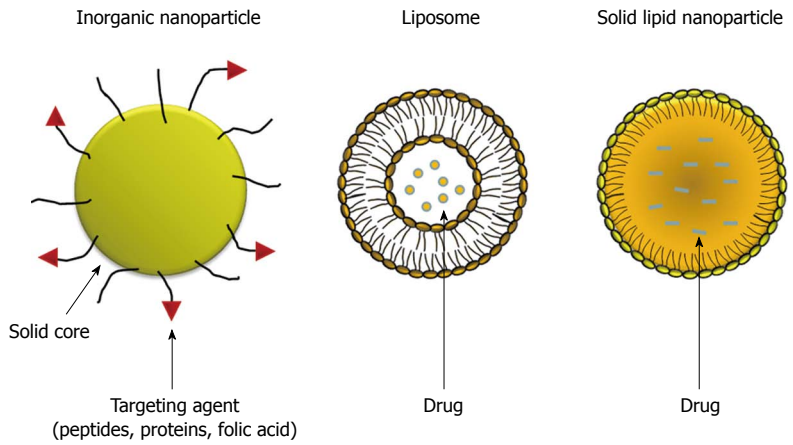

Figure 1 Major types of nanoparticles including: inorganic nanoparticles, liposomes and solid lipid nanoparticles.

of their outstanding properties. Generally, inorganic nanoparticles can be defined as particles with a metal oxide (iron oxide, titanium oxide, *etc.*) or metal (gold and silver) central core and with a protective organic layer on the surface. The organic outer layer both protects the core from degradation and also allows the conjugation of biomolecules with reactive groups (amines and thiols) to link peptides, proteins and folic acid (Figure 1). In recent years inorganic NPs have gained significant attention due to their unique material- and size-dependent physicochemical properties, which are not possible with organic NPs. Their unique optical, magnetic and electronic properties can be tailored by controlling the composition, size, shape, and structure. In some cases, inorganic nanoparticles are attractive alternatives to organic NPs for drug delivery and imaging a specific tissue because of their physical features, such as optical and magnetic properties, in addition to their inertness, stability and easy functionalization[10-13].

Polymeric NPs, liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) form a large and well-established group of organic nanoparticles (Figure 1). These biodegradable, biocompatible polymeric NPs have attracted significant attention as potential drug delivery systems since they can be applied in drug targeting to particular organs/tissues and as carriers of DNA in gene therapy, and are also able to deliver proteins and peptides via oral administration.

Biodegradable natural polymers include chitosan, albumin, rosin, sodium alginate and gelatin, while synthetic polymers include polylactic acid (PLA), polylactic-glycolic acid (PLGA), polycaprolactones (PCL), polycyanoacrylates and polyaminoacid conjugates)[14-17]. PLA and PLGA biodegradable polymeric nanoparticles have recently been approved by the US Food and Drug Administration for human use.

Liposomes are spherical artificial vesicles consisting in one or more phospholipid bilayers enclosing an aqueous compartment. Liposomes can encapsulate a wide variety of lipophilic (hydrophobic) and hydrophilic drugs within their dual compartment structure. Hydrophobic drugs can be incorporated into the bilayer, while hydrophilic drugs can be contained within the inner aqueous core formed by the lipid membrane. NPs made with liposomes are the simplest form of NPs and have several advantages, such as easy preparation, good biocompatibility, reduced systemic toxicity and increased uptake[11,18]. Conventional liposomes, termed "non-stealth" liposomes, are rapidly removed from the blood circulation because of their high affinity for the RES. However, this phenomenon has been avoided by coating them with hydrophilic molecules (such as PEG derivatives) linked to the liposomal formulation by a lipid anchor. This modification significantly prolongs liposome circulation over time[19], and therefore improves pharmacological potency, reduces the dose and widens the range of indications.

In the early 1990s a new class of colloidal drug carriers, SLNs, were developed[20]. SLNs have been reported to be an alternative carrier system to emulsions, liposomes and polymeric nanoparticles. SLNs are particles measuring above the submicron range (from about 50 to 500 nm). SLNs are produced by substituting the liquid lipid (oil) with a solid lipid, *i.e.*, the lipid is solid at both room and human body temperatures. SLN are mainly composed of physiological solid lipid dispersed in water or, if necessary, in aqueous surfactant solution. The solid lipid core may contain triglycerides, glyceride mixtures, fatty acids, steroids or waxes. SLNs offer the advantages of the traditional systems but avoid some of their major disadvantages. SLNs are relatively easy to produce without the use of organic solvents, and may be produced on a large scale at low cost[21]. They do not cause toxicity or biodegradability problems, being obtained from physiological lipids and, since the mobility of a drug in solid lipid is lower compared to that in liquid lipid, they can control drug release[22-27].

NLCs were developed at the end of the 1990s to overcome some limitations related to older generation SLNs[25,27,28]. NLCs are produced using blends of solid lipids and liquid lipids (oils), the blends being solid at room and body temperatures. Both NLCs and SLNs are made of physiological, biodegradable, and biocompat-

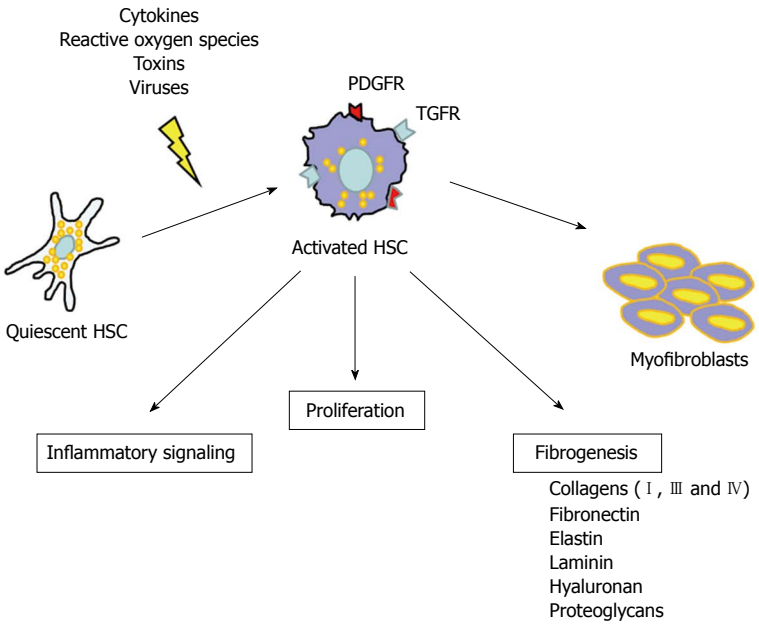

Figure 2 Quiescent stellate cell activation is initiated by different types of stimulus (cytokines, reactive oxygen species, toxins, viruses). The activated cell is transformed into myofibroblasts which contain contractile filaments. Activation of hepatic stellate cells is associated with a gradual replacement of the extracellular matrix (ECM) by the collagen rich fibers and the production of fibrous bands. In advanced stages of fibrosis, the liver contains more ECM components than normal, including collagens (Ⅰ, Ⅲ and Ⅳ), fibronectin, elastin, laminin, hyaluronan, and proteoglycans. PDGFRs: Platelet-derived growth factor receptors; TGFR: Transforming growth factor receptor.

ible lipids and surfactants. NLCs, similar to SLNs, are colloidal particles ranging in size from 100 to 500 nm. Compared to SLNs, NLCs possess a higher drug loading capacity, lower water content, reduced drug expulsion during storage and longer physical stability[22,23-31].

TREATMENT OF LIVER FIBROSIS BY NANOTECHNOLOGY APPROACHES

Liver fibrosis is an abnormal liver condition in which there is a scarring of the liver. It is the consequence of a chronic liver injury and a continual wound-healing process mainly triggered by hepatitis viruses (HBV and HCV) chronic infection, alcohol consumption, genetic abnormalities, steatohepatitis, autoimmune damage, *etc*. Key players in the fibrotic process, which takes place at the cellular and molecular levels, are the HSCs. Their activation and transformation into myofibroblasts, initiated by different types of stimuli, such as cytokines[32], reactive oxygen species[33], toxins[34] and viruses[35], determine an overproduction of extracellular matrix (mainly type I and Ⅲ collagens) which greatly contributes to intrahepatic connective tissue expansion during fibrogenesis (Figure 2). Moreover, activated HSCs secrete pro-fibrotic and pro-inflammatory mediators which perpetuate their activated state, and due to their contractile features they also play a pivotal role in the portal hypertension setting, the major cause of clinical complications of liver cirrhosis[36,37].

In the clinical setting, the conventional anti-fibrotic treatments are still limited, often due to non-specific drug disposition. Thus, the aim of efficient antifibrotic drug delivery using nanotechnology approaches is to achieve liver-specificity with subsequent targeting of the fibrotic region. In this context, HSCs have been the major target for delivering drugs to fibrosis using nanotechnology approaches (Figure 3).

The strongest experimental evidence on possible new approaches for the treatment of liver fibrosis derives from the use of different HSC-selective nanoparticle carriers, most of which are based on the conjugation of targeting ligands directed against receptors expressed by activated HSCs at the surface of various types of NPs. In fact, activated HSC cells express or over-express various receptors, such as mannose-6-phosphate/insulin-like growth factor Ⅱ (M6P/IGF Ⅱ) receptor, PPARs, integrins, platelet-derived growth factor receptors (PDGFRs), retinol binding protein (RBP) receptor and galactosyl receptor, which could be the target of NPs.

M6P/IGF Ⅱ receptor

M6P/IGF Ⅱ receptor is involved in the activation of latent transforming growth factor β (L-TGFβ). M6P/IGF Ⅱ receptor is highly and specifically up-regulated on activated HSC during liver fibrosis[38,39]. TGFβ is a fibrogenic cytokine with many functions, including collagen production and inhibition of its degradation[40]. TGFβ binds to the TGFβ type-Ⅱ receptor on the cell surface, which then heterotetramerizes with a type-I receptor, in most cases activin-like kinase 5. Several preclinical results using different animal models of liver fibrosis suggest that selective localization of a drug to HSC can be possible by targeting the M6P/IGF Ⅱ receptor. First, Beljaars *et al*[41] demonstrated that in rats with liver fibrosis M6P-human serum albumin (albumin chemically modified with 28 M6P groups, M6P-HSA) could be taken up and selectively accumulated in activated HSC. The binding of M6P-HSA to HSC was specific and mediated by binding to M6P/IGF-Ⅱ receptor. This first evidence therefore suggested that M6P-HSA is a suitable carrier for the selective delivery of antifibrotic drugs to activated HSC. Based on these findings, Adrian *et al*[42,43] coupled M6P-HSA to the surface of liposomes and injected them via the penile vein in rats with liver fibrosis induced by bile

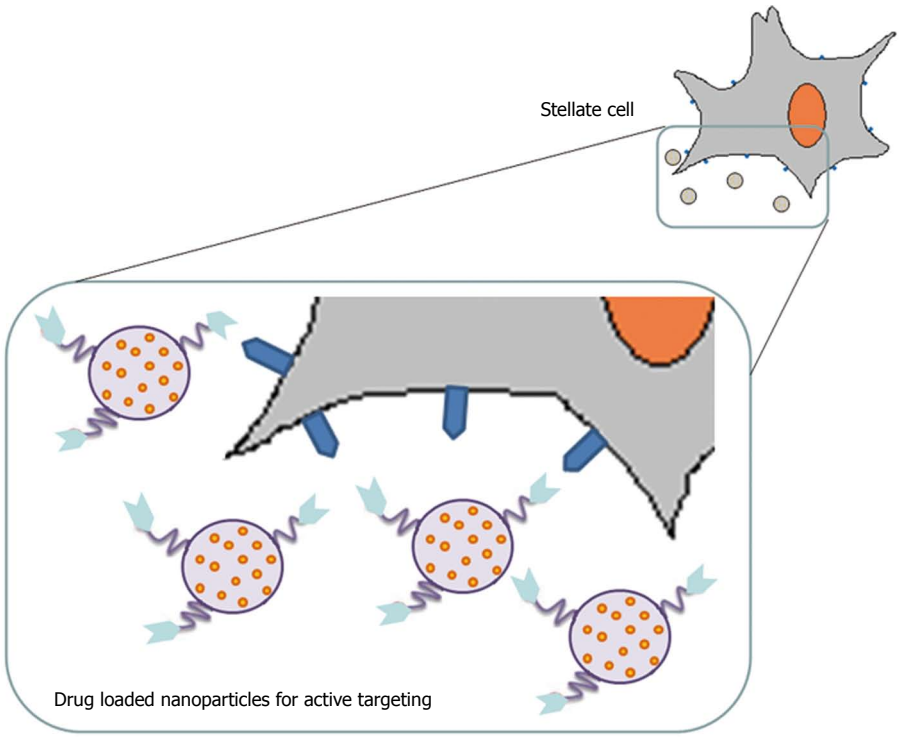

Figure 3 Nanoparticles are loaded with drugs to actively target the disease site by using cell-specific homing devices.

duct ligation. M6P-HSA liposomes were rapidly cleared from the blood circulation in the diseased rats and mainly accumulated in the liver. These studies demonstrated that liposomes coupled with M6P-HSA are potentially effective drug carriers and therefore open up new possibilities for pharmacological interference with a disease as complex as liver fibrosis. Subsequently, to explore new potential therapeutic interventions based on a genetic approach for the treatment of liver fibrosis, inactivated hemagglutinating virus of Japan (HVJ, also known as Sendai virus) containing plasmid DNA was fused with M6P-HSA liposomes to yield HVJ liposomes that selectively target HSCs[43]. Adrian *et al*[44], showed that following *iv* injection into mice with liver fibrosis, M6P-HSA-HVJ-liposomes efficiently associated with HSC. This approach therefore offers new possibilities for treating liver fibrosis.

PPARs

PPARs, which belong to the superfamily of nuclear hormone receptors with transcriptional activity controlling multiple processes, have been implicated in liver fibrogenesis[45]. To date, four isoforms of PPARs have been identified, namely PPARδ, β, γ and δ. Growing evidence shows that activated HSCs express PPARδ and its expression exerts important effects on fibrogenesis in animal models[46], and that treatment with PPARδ ligands, Wy-14643 (WY) or fenofibrate, dramatically reduces hepatic fibrosis[47]. PPARβ and PPARδ are also highly expressed in HSCs, and their activation increases hepatic fibrosis[48]. There is clear evidence that activation of HSCs and their transdifferentiation into myofibroblasts is accompanied by significantly decreased PPARγ expression, and that treatment with PPAR-γ agonist rosiglitazone inhibits HSC activation[49]. Therefore, PPARs are considered a promising drug target for antifibrotic therapy[50-52]. M6P-HSA-conjugated liposomes have also been used to deliver ligands for PPAR to activated HSCs. Recently, Patel *et al*[53] reported a significant enhancement of liver uptake, improvement in histopathological morphology and decreased fibrosis grade when the PPARγ ligand rosiglitazone was loaded in M6P-HSA-conjugated liposomes and administrated intravenously in rats with liver fibrosis.

Integrins

Activated HSCs express increasing amounts of integrins. Integrins are a large family of heterodimeric cell surface receptors which mediate the interaction between cells and extracellular matrix molecules (such as collagens and fibronectin) and recognize a common motif in their ligands, among which the best studied is the RGD sequence (arginine-glycine-aspartic acid)[54-56]. Collagen VI, abnormally produced in the liver by activated HSCs and deposited during fibrogenesis, is recognized by cell-surface integrins, mainly integrin δ1β1, through the specific interaction of the receptor with the RGD sequence present in the matrix molecule. Therefore, the RGD sequence has been used as a homing device to target integrins and hence HSCs in fibrotic liver. In 2000 a carrier which showed binding and internalization to HSC was successfully used for the first time[57], suggesting the possibility to deliver anti-fibrotic agents directly to HSC. Subsequently, Du *et al*[58] developed cyclic RGD-labeled sterically-stabilized liposomes (SSLs) to deliver IFNδ-1b to HSC. They demonstrated that cyclic RGD peptide-

labeled liposomes were selectively taken up by activated HSCs in a liver fibrosis rat model, and that liposome encapsulated IFNδ-1b displayed an improved efficiency in blocking fibrogenesis. In another study, Li *et al*[59] also used SSLs labeled with cyclic RGD peptide to encapsulate hepatocyte growth factor (HGF), in order to prevent its degradation and therefore to reverse fibrogenesis processes[60]. When HGF was encapsulated in SSL labeled with cyclic RGD peptide (RGD-SSL-HGF) it was more effective than SSL-HGF in promoting liver fibrosis regression in cirrhotic rats, indicating that HGF loaded in RGD-SSL enhanced its effect on activated HSCs[60].

PDGFRs

PDGF is the most potent proliferative factor in liver fibrosis. Its receptor (PDGFR) has two forms, PDGFRδ and PDGFRβ. PGFRs are cell surface tyrosine kinase receptors for members of the PDGF family. In particular, PDGF-β receptor is highly upregulated on activated HSCs[61]. Recent studies in rats with hepatic fibrosis showed that pPB-SSL-IFN-γ, a targeted SSL modified by a cyclic peptide (pPB) with affinity for the PDGF-β receptor to deliver IFN-γ (pPB-SSL-IFN-γ) to HSCs, improves the anti-fibrotic effects of IFN-γ and reduces its side effects to some extent[62,63].

RBP receptor

RBP receptor expressed by HSCs, is involved in the uptake and storage of vitamin A. Sato *et al*[64] assessed the anti-fibrotic properties of vitamin A-coupled liposomes containing small interfering RNA (siRNA) against gp46, the rat homolog of human heat shock protein 47 and involved in the inhibition of collagen secretion, in three experimental models of liver fibrosis induced by dimethylnitrosamine, carbon tetrachloride (CCl_4), and bile duct ligation. They showed that the treatment decreased collagen deposition, induced apoptosis of HSCs, improved liver function tests and prolonged survival in the treated rats.

Galactosyl receptor

Hepatic fibrosis is also the result of oxidative damage to the liver due to exposure to environmental metalloid toxicants. Therefore, a promising strategy has been developed to deliver antioxidants to damaged liver by nanocarriers. The galactosyl receptor expressed on the hepatocytes mediates the internalization of molecular asialoglycoproteins and small particles. With this in mind, liposomes decorated with p-aminophenyl δ-*D*-galactopyranoside, which binds to galactosyl receptor, have been used as carriers for targeted *iv* delivery of the antioxidant flavonoid quercetin (QC) in animals with liver fibrosis[65,66]. It has been shown that the administration of QC loaded in galactosylated liposomes in rats results in the maximum prevention of arsenic deposition (a contaminant responsible for oxidative damage present in drinking water, particularly in developing countries such as India and Bangladesh) and protects the liver from sodium arsenite ($NaAsO_2$)-induced collagen deposition and fibrosis initiation. However, whereas free QC does not protects rats from oxidative damage, galoctosylated liposomes QC might be therapeutically useful to prevent $NaAsO_2$-induced acute liver toxicity.

Apoptosis-inducing agents

Oxymatrine (OM) is an alkaloid extracted from the medicinal plant *Sophora alopecuroides L.* which, among its multiple pharmacological functions, can induce apoptotic cell death in different cell types[67,68] and exerts antiviral effects, inhibiting HBV and HCV replication[69,70]. In addition, OM has also been demonstrated to have anti-fibrotic effects, being effective in reducing collagen production and deposition in CCl_4-induced liver fibrosis in rats[71]. Based on these findings, Chai *et al*[72] used OM-RGD liposomes in both *in vitro* and *in vivo* experiments and demonstrated that delivery of OM to HSCs with this formulation attenuates hepatic fibrosis by inhibiting viability and inducing HSC apoptosis, thus highlighting its possible application in the treatment of hepatic fibrosis. The influence of OM on the fibrotic process has also been evaluated in a bile duct ligation rat model of liver fibrosis using self-assembled polymeric vesicles based on biodegradable poly(ethylene glycol)-b-poly(e-caprolactone) (PEG-b-PCL), referred to as polymersomes (PM), and modified with RGD peptide to obtain RGD-PM-OM[73]. Yang *et al*[73], demonstrated that intravenous injection of RGD-PM-OM and PM-OM formulations showed significant benefits in ameliorating the degree of liver injury and fibrosis as shown by lower levels of fibrosis markers in the serum compared to free OM. This novel approach therefore appears to be more effective than conventional treatment with OM.

Curcumin or diferuloylmethane, a yellow polyphenol extracted from the rhizome of turmeric *Curcuma longa*, has been extensively studied for its therapeutic effects in a variety of disorders because of its antineoplastic, antioxidant and anti-inflammatory effects[74-76]. Several studies have shown its potential anti-fibrotic activity[77-84] but the compound has poor aqueous solubility, which results in low bioavailability and low concentrations at the target site[85,86]. Consequently, nanotechnology approaches have been developed to deliver curcumin to targets. For example Bisht *et al*[87] developed a polymeric nanoparticle formulation of curcumin (NanoCurc™). Nanocurcumin was synthesized utilizing the micellar aggregates of cross-linked and random copolymers of *N*-isopropylacrylamide, with *N*-vinyl-2-pyrrolidone and poly(ethylene glycol) monoacrylate (PEG-A). Nanocurcumin showed to be readily dispersed in aqueous media with a comparable *in vitro* therapeutic efficacy to free curcumin against a panel of human cancer cell lines[87]. The same authors subsequently performed *in vivo* studies using NanoCurc™ to treat animals with hepatic injury and fibrosis induced by CCl_4 administration[88]. Results following intraperitoneal injection of NanoCurc™ were extremely promising, as NanoCurc™ enhanced the bio-

availability of intrahepatic curcumin concentrations compared to control void NPs, attenuated hepatocellular injury and levels of pro-inflammatory cytokines, inhibited CCl_4-induced liver injury, prevented hepatic fibrosis and induced HSC apoptosis. The exact mechanism by which curcumin induces a protective hepatocellular environment is not clear. Curcumin might work through multiple mechanisms. As reported by Bisht *et al*[88] NanoCurc™ accumulates in hepatocytes and in the non-parenchymal cell compartment, which contains pro-fibrotic stellate cells and myofibroblasts. Authors have demonstrated that NanoCurc™ inhibits pro-fibrogenic transcripts associated with activated myofibroblasts and directly induces HSC apoptosis. However, another possibility is that NanoCurc™ might also affect hepatic progenitor cells or bile duct cells and thus ameliorate the effects of CCl4-induced liver injury by influencing these cells.

CONCLUSION

The extremely wide diffusion of CLD worldwide and the relatively ineffective therapeutic options especially for advanced liver fibrosis demand new drugs or new drug delivery strategies to cure liver fibrosis. Therapies based on nanotechnologies have emerged as an innovative and promising alternative to conventional therapies. The number of NPs used in biomedical research and drug delivery is rapidly increasing. Several reports in the literature, most of all in animal models, have shown that different HSC-selective NP carriers, based on the conjugation of targeting ligands directed against several receptors expressed by activated HSCs at the surface, can reduce liver fibrosis. These data, if confirmed in humans, could open up a new era in the treatment of liver fibrosis. In the next few years the clinical validation of CLD therapies based on nanotechnologies will hopefully be demonstrated.

However, much more needs to be done, particularly because the use of nanoparticles also creates unique environmental and societal challenges[89]. Toxicity associated with nanomaterials should be considered before NPs are widely utilized as drug delivery systems, especially for inorganic nanoparticles[90,91]. In this respect, the risk associated with organic NPs seems to be less problematic because this type of nanoparticles are very often typically either made from, or covered with natural or highly biocompatible polymers (such as PEG)[92].

Finally, it is necessary to develop a regulatory framework based on objective scientific research which will ensure that human exposure to unwanted engineered nanomaterials in the environment will be limited to safe levels. However, the therapeutic use of nanomaterials in medicine requires a different framework in which the therapeutic benefits will be balanced against the potentially harmful risks.

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