EXPERT OPINION

Novel materials which possess the ability to target liver cells

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Introduction: Hepatic-targeted drug delivery systems are designed to treat diseases of the liver. However, since there are several different types of liver diseases that are caused by different cells, it is important to select the proper materials to target these different cells.

Areas covered: This review addresses novel materials that possess the ability to target liver cells via receptor–ligand processes and offers an insight into the aspects of formulation design. It also discusses several approaches used to enhance the targeting efficiency of drug delivery systems to receptors in the liver cells. In addition, the delivery efficiency and therapeutic efficacy of these materials in the treatment of acute or chronic liver diseases is highlighted.

Expert opinion: Further research into the use of clinical materials and the design of smart materials for multi-drug delivery to different organelles is important for future studies on these new materials. It is hoped that these targeted therapeutics will benefit patients with liver disorders in the near future.

Keywords: hepatic non-parenchymal cell, hepatic parenchymal cell, liver targeting, novel material

Expert Opin. Drug Deliv. (2012) 9(6):649-656

1. Introduction

At present, liver diseases such as hepatic cancer, hepatic cirrhosis and hepatic fibrosis are encountered quite frequently in clinical practice. The hepatic cells are composed of hepatic parenchymal and hepatic non-parenchymal cells. Liver functions such as metabolism, bile production and glycogen synthesis are performed by hepatic parenchymal cells, which are damaged by various pathological processes. The hepatic parenchymal cells produce inflammatory mediators such as free radical species and cytokines when damaged. These mediators initiate many pathological cascades such as fibrogenesis and cancers [1].

Primary hepatic carcinoma, which occurs in hepatic cells or intrahepatic bile ducts, is usually called hepatic cancer. The analysis of global tumor statistics by the World Health Organization indicates that about 130,000 people have died because of hepatic cancer and that the incidence is 5 – 10 times higher than in European and American countries. Hepatic cancer has a higher recurrence rate and shorter survival time, which makes it the second leading cause of cancer death after stomach cancer.

To selectively target drugs to hepatocytes, a technique called hepatic-targeted drug delivery system (HTDDS) is used; this system uses a variety of vehicles, such as liposomes, nanoparticles, albumin, lipoproteins, microspheres, emulsions, polymer conjugates and recombinant chylomicrons, which are actively absorbed by the liver. With the discovery of the HTDDS, rapid progress has been made in the development of targeted drug delivery systems, especially receptor–ligand drug targeting systems. The HTDDS selectively distributes drugs to the liver, thus not only enhancing their bioavailability but also reducing the side effects of targeting.

10.1517/17425247.2012.679261 © 2012 Informa UK, Ltd. ISSN 1742-5247

The non-parenchymal cells are composed of Kupffer cells (KCs), sinusoidal endothelial cells (SECs) and hepatic stellate cells (HSCs). The KCs are one of the members of the body's defense system, which can phagocytize and clear foreign bodies in the blood.

Liver fibrosis is a disorder that is characterized by deposition of large amounts of extracellular matrix (ECM) components like collagens. The fibrotic process is induced by the concerted action of many cell types. Inciting stimuli may damage hepatocytes and cause the activation of other resident hepatic cells like KCs, SECs, HSCs and so on. The KCs play an important role in continuing the inflammatory process [2]. To ensure more KC-specific uptake, it is necessary to synthesize new conjugates.

Some studies have shown that the HSCs play an important role in the initiation and propagation of inflammatory reactions. HSCs may cause increased ECM deposition. So these types of cells are important targets for pharmacotherapeutic intervention [3,4].

In summary, different hepatic diseases are caused by different cells. So it is important to design or select proper materials to target these different cells. The present review covers several approaches used to enhance the targeting efficiency of drug delivery systems to receptors in the liver. In addition, their delivery efficiency and therapeutic efficacy in the treatment of acute or chronic liver diseases are discussed.

2. Studies of receptors and ligands

Ligands have been investigated quite extensively. It is well known that there are many receptors present on the surface of hepatic cells. An abundant receptor specific to hepatic parenchymal cells is the asialoglycoprotein receptor (ASGP-R), which can recognize the galactosylated ligand, lactobionic acid (LA) ligand, asialofetuin (AF) ligand, soybean-derived sterylglucoside (SG) ligand and so on. Glycyrrhetinic acid (GA) receptor, predominantly expressed on the sinusoidal surface of mammalian hepatocytes, has also been studied recently. It can recognize the GA ligand. The hepatic non-parenchymal cells also contain many receptors, such as the mannose receptors, that are located on the surface of the KCs.

A number of suitable strategies for liver-selective targeting systems have been developed that involve the use of mannose, which is chemically modified with substrates or ligands (such as sugars and peptides) that bind receptors on the surface of hepatocytes. Among these, chemically mannosylated (Man)-albumins have received considerable attention because of albumin receptors, which specifically recognize ligands containing a terminal non-reducing D-mannose [5-7], *N*-acetylglucosamine or L-fucose and are expressed mainly on non-parenchymal liver cells, including KCs and SECs (**Table 1**) [8].

Therefore, to attenuate liver injury, inhibit hepatitis or modify hepatocyte-related metabolism, therapeutic agents should ideally be delivered to the liver, especially to the hepatic parenchymal or hepatic non-parenchymal cells.

3. Hepatic parenchymal cell targeting materials

3.1 ASGP-R targeting materials

ASGP-R, which is located on the surface of hepatic parenchymal cells, is responsible for the clearance of glycoproteins with desialylated galactose or acetylgalactosamine residues from the circulation by receptor-mediated endocytosis [9]. The galactose-binding extracellular domain belongs to the long-form subfamily with three conserved intramolecular disulfide bonds. It is able to bind terminal non-reducing galactose residues and *N*-acetylgalactosamine residues of desialylated tri- or tetra-antennary N-linked glycans. Many scientists have synthesized materials that contain desialylated galactose or acetylgalactosamine residues to improve the targeting of drug delivery.

3.1.1 Galactosylated ligand

Galactosylated- and fluorescein isothiocyanate (FITC)-labeled polycaprolactone-g-dextran (Gal-PCL-g-Dex-FITC) polymers were synthesized by Wu *et al.* [10]. The results showed that after the injection of Gal-PCL-g-Dex-FITC-1 micelles, the liver showed a 30% absorption while the other tissues showed only a 10% increase in the concentration. Although the untargeted micelles were absorbed by liver, this percentage was much lower when compared with that of the targeted micelles. Apparently, the Gal-PCL-g-Dex-FITC-1 micelles were absorbed to a greater extent by the mouse liver.

Zheng *et al.* [11] characterized the chemical structure of lactosaminated carboxymethyl chitosan (LAC-CMC), which was synthesized by a reductive amination reaction [12]. Glycyrrhizic acid was chosen as the model drug and encapsulated within LAC-CMC nanoparticles through ionic gelification. In an experiment to determine the tissue distribution in mice, glycyrrhizic acid from LAC-CMC nanoparticles attained a maximum concentration of 47.82 μg/ml in the liver at 4 h post-injection, which was significantly higher than that achieved with traditional nanoparticles and glycyrrhizic acid solutions.

3.1.2 LA ligand

Wang *et al.* [13] synthesized a novel galactosylated lipid with a mono-galactoside moiety, (5-cholesten-3b-yl) 4-oxo-4-[2-(lactobionyl amido) ethylamido] butanoate (CHS-ED-LA), and used it in the selective targeting of doxorubicin (DOX), a model drug. Results showed that the galactosylated liposomes gave a relatively high liver targetability value of 64.6%, while DOX in the conventional liposome only gave a value of 21.8%. The carriers modified by the novel materials could deliver about three times more DOX to the liver than the conventional liposome.

Kamruzzaman Selim, *et al.* [14] studied superparamagnetic magnetite nanoparticles whose surface was modified with LA to improve their intracellular uptake and hepatic parenchymal cell targeting. Cell culture experiments showed that LA-modified nanoparticles were internalized into

Table 1. The different receptors and ligands present on the surface of hepatic cells.

	Receptor	Ligand
Hepatic parenchymal cells	Asialoglycoprotein	Galactosylated Lactobionic acid Asialofetuin Soybean-derived sterylglucoside
	Glycyrrhetinic acid	Glycyrrhetinic acid
	Bile acid	Bile acid
Hepatic non-parenchymal cells		
Kupffer cells	Mannose receptor	Mannose
Hepatic stellate cell	PDGF M6P/IGF-II	M6P

IGF-II: Insulin-like growth factor II; M6P: Mannose-6-phosphate; PDGF: Platelet-derived growth factor.

hepatocytes, and atomic absorption spectrometer measurements indicated that the uptake amount of LA-modified magnetite into hepatic parenchymal cells was higher than that of unmodified magnetite.

3.1.3 *AF ligand*

AF, a natural ligand for ASGP-R, is a glycoprotein that possesses three asparagine-linked triantennary complex carbohydrate chains with terminal LacNAc (*N*-acetyllactosamine) residues. The protein displays affinity to hepatocyte ASGP-R and is endocytosized by the cells. Its receptor dissociation constant is 200-fold lower than the glycoproteins with biantennary N-linked oligosaccharide chains. Therefore, it has been used as a competitive inhibitor to other polysaccharides that also have affinity to the receptors. Keiichi *et al.* [15] synthesized AF-appended cationic liposomes (CLs) (AF-liposomes) associating cyclodextrins (CyD/AF-liposomes) as a hepatocyte-selective non-viral vector. AF-liposomes associated with plasmid DNA (pDNA) and γ-cyclodextrin (γ-CyD) (pDNA/γ-CyD/AF-liposomes) showed the highest gene transfer activity in HepG2 cells without any significant cytotoxicity.

Gagandeep [16] developed poly(D,L-lactic-co-glycolic acid) nanoparticles using the double emulsion method. To improve the targeted delivery into hepatic parenchymal cells, the nanoparticles were coated with AF. Meanwhile, covalently conjugated protein on nanoparticles was labeled with rhodamine and used for cell-based studies. Results from these studies indicated that AF conjugated with nanoparticles showed enhanced and selective uptake by hepatic parenchymal cells compared with nanoparticles conjugated with bovine serum albumin.

3.1.4 *Soybean-derived SG ligand*

Soybean-derived SG is a residue extracted from soybeans. Qi *et al.* [17] developed CLs with SG and polyethylene glycol (C/SG/PEG-liposomes) and compared them with other liposomes. C/SG-liposomes-entrapped fluorescein sodium (FS) was effectively transfected into HepG2 2.2.15 cells *in vitro*. C/SG/PEG-liposomes-entrapped antisense oligonucleotides (ODNs) reduced the secretion of both HBsAg and HBeAg in HepG2 2.2.15 cells when compared with free ODNs. After *in vivo* injection of ^{3}H-labeled C/SG/PEG-liposomes, higher radiation accumulation was observed in the parenchymal cells than non-parenchymal cells of the liver. From the results, it was evident that the liposome may have selective access to parenchymal cells when modified by SG.

Maitani *et al.* [18] also developed a formulation generated from dipalmitoylphosphatidylcholine (DPPC), cholesterol (Chol) and SG in a molar ratio of 6:3:1, used it to entrap a chemotherapeutic agent, DOX, and investigated the liposome-mediated DOX incorporation in HepG2 cells. The results showed that compared with conventional liposomes, the novel liposomes could deliver more DOX to the parenchymal cells. This suggests that the DPPC-Chol-SG liposome-mediated delivery of DOX into cells is probably achieved through ASGP-R-mediated endocytosis. Thus, SG may work as a potential ligand to label liposomes for hepatocyte targeting, and SG-liposomes are potentially useful drug carriers to parenchymal cells in the liver [18].

3.2 GA receptor targeting materials

GA, which has saturability and specificity, is located on the surface of hepatic parenchymal cell membranes. There is significant interest in the use of GA as a ligand-modifying drug carrier in hepatic parenchymal cells.

GA is the main bioactive compound in licorice (*Glycyrrhiza glabra* L.), which is widely used in medicine for the treatment of many pathologies [19,20] owing to its anti-inflammatory, anti-gastric, anti-hepatitis, anti-allergic and anti-hepatotoxic effects. It is one of the main compounds extracted from the root of licorice [21], which is known to inhibit liver carcinogenesis and cell proliferation in the human hepatocellular carcinoma (HCC) cell line HepG2 [22]. It has been proved that protein kinase C (PKC) α, the target binding site of GA, is expressed more highly in HCC cells than in the adjacent non-tumor live cells.

He *et al.* [23] developed the GA-modified stealth CLs (GA–PEG–CLs) loaded with pDNA (GA–PEG–CLPs) and found that they transfect the HCC cell line HepG2 with high efficiency. Compared with ordinary CLs, steric CLs

(PEG–CLs) and 1% GA–PEG–CLs, 5% GA–PEG–CLs were found to possess the highest transfection efficiency as gene vectors in serum-free or serum-containing medium in PKCα overexpressed HepG2 cells but showed no significant difference in the human embryonic kidney cell line HEK 293. Additionally, 5% GA–PEG–CLs have the lowest cytotoxicity in normal human hepatocyte cell line L02. The competitive inhibition experiments mediated by GA were carried out in HepG2 cells, which demonstrated that GA–PEG–CLs could selectively deliver pDNA to hepatoma cells using the GA targeting moiety. In conclusion, GA–PEG–CLs containing 5% GA–PEG–Chol might be a gene vector with good potential as a hepatoma-targeting therapy.

Tian *et al.* [24] prepared chitosan/poly(ethylene glycol)-GA (CTS/PEG-GA) nanoparticles by an ionic gelation process in which GA acts as the targeting ligand. The accumulation of the CTS/PEG-GA nanoparticles in the liver was 51.3% at 3 h after injection, which was nearly 2.6 times of that obtained with the CTS/PEG nanoparticles, showed a high level during the experiment. This observation was also confirmed using single-photon emission computed tomography. The concentration of CTS/PEG-GA nanoparticles in the liver was much higher than in the other organs at 15, 90 and 180 min, and much lesser in the kidney and bladder. No obvious decrease in relative radioactivity in the liver was observed until the end of the measurement. By contrast, the non-targeted CTS/PEG nanoparticles were mainly localized in the kidney, bladder and the liver and their concentration decreased gradually over time, while the total radioactivity in the kidney and bladder increased.

3.3 Bile acid receptor targeting materials

Bile acids and bile acid receptors are therapeutic targets in the development of drugs for the treatment of cholestatic and fatty liver diseases. In the liver, bile acids activate a nuclear receptor, farnesoid X receptor (FXR), which induces an atypical nuclear receptor small heterodimer partner. Bile salt-coated liposomes can successfully be delivered to the liver [25]. Chen *et al.* [26] modified phospholipid (PC)/Chol liposomes using a novel polymer bile salts-(polyethylene glycol)2000-bile salt (BP_2B) by the *N*,*N*′-dicyclohexylcarbodiimide (DCC)/4-dimethylaminopyridine (4-DMAP) esterification method. The results showed that the mean residence time of the liposomes (BP_2BL), which included BP_2B, was longer than that of traditional liposomes (CL), although it was statistically not significant ($p > 0.05$). The mean plasma concentration–time profile of BP_2B was higher than that of CLs and suggested a state of slow release of BP_2B.

4. Hepatic non-parenchymal cell targeting materials

4.1 Mannose receptor targeting materials

Mannose receptors are known to contribute to the defense mechanism of mammals by endocytosis or phagocytosis of terminal mannose bearing exogenous materials [27].

Mannosylated chitosan-ZnS nanocrystals (NCs) were prepared by a two-step process involving i) *in situ* synthesis of chitosan-ZnS NCs and ii) mannosylation of the prepared NCs [28]. The nanobioconjugates possessed high colloidal stability and strong fluorescence emission at 600 nm. Characterization using X-ray diffraction, dynamic light scattering, scanning electron microscope, atomic force microscopy and Fourier transformed infrared spectroscopy revealed that the bioconjugated particles were appropriately functionalized and stable, with an average size 150 nm.

Rieger *et al.* [29] reported the synthesis of fully biodegradable polymeric nanoparticles presenting mannose residues at their surface and their interaction with lectins, a simple and versatile method that achieved the surface functionalization of poly(D,L-lactic acid) (PLA) nanoparticles using mannose moieties. It uses an amphiphilic mannosylated poly(ethylene oxide)-b-poly(E-caprolactone) (PEO-b-PCL) diblock copolymer as a bioresorbable surface modifier in a simple nanoprecipitation-evaporation procedure. The size and zeta potential of the nanoparticles were found to depend on the molar copolymer/PLA ratio, demonstrating the influence of the copolymer on the formation of the nanoparticles. The targeting properties of these carrier systems, combined with their potential adjuvant effects owing to their size in the range of 200 - 300 nm, make them attractive candidates as vaccine delivery systems.

In gene delivery systems, Chuang *et al.* [30] synthesized a novel mannosylated Chol derivative, cholesten-5-yloxy-*N*-(4-((1-imino-2-b-D-thiomannosylethyl)amino)alkyl) formamide (Man-C4-Chol), for gene delivery to macrophages that are known to express large numbers of mannose receptors on their surface [29,31]. For *in vitro* gene delivery, hepatic non-parenchymal cells seem to be more efficient target cells than hepatic parenchymal cells because the DNA–CL complexes can more easily access the target cells in this case.

These results suggest that pDNA complexed with mannosylated liposomes exhibits the high transfection activity in hepatic non-parenchymal cells due to recognition by mannose receptors. This may be due to KCs that are present around the sinusoidal membranes; therefore, selection of the administration route must be considered for efficient targeted delivery of pDNA [32].

Human serum albumin (HSA), a non-glycosylated protein, is the most abundant protein in the plasma. HSA possesses multiple functions, including the maintenance of colloid osmotic pressure in the plasma and the transport of various endogenous substances and metabolites [33]. Thus, HSA is widely used as a versatile carrier in drug delivery systems to improve pharmacokinetics and stability [34,35].

Kenshiro *et al.* [36] prepared mannosylated-HSA mutants (Man-rHSAs: D63N, A320T and D494N) and their triple mutant (TM-rHSA: D63N/A320T/D494N). Man-(12)-HSA was synthesized by reacting HSA with 2-imino-2-methoxyethyl 1-thioglycomannoside as previously described [37]. A pharmacokinetic analysis of ^{111}In-Man-rHSAs in mice showed that they were rapidly cleared from the blood circulation and were

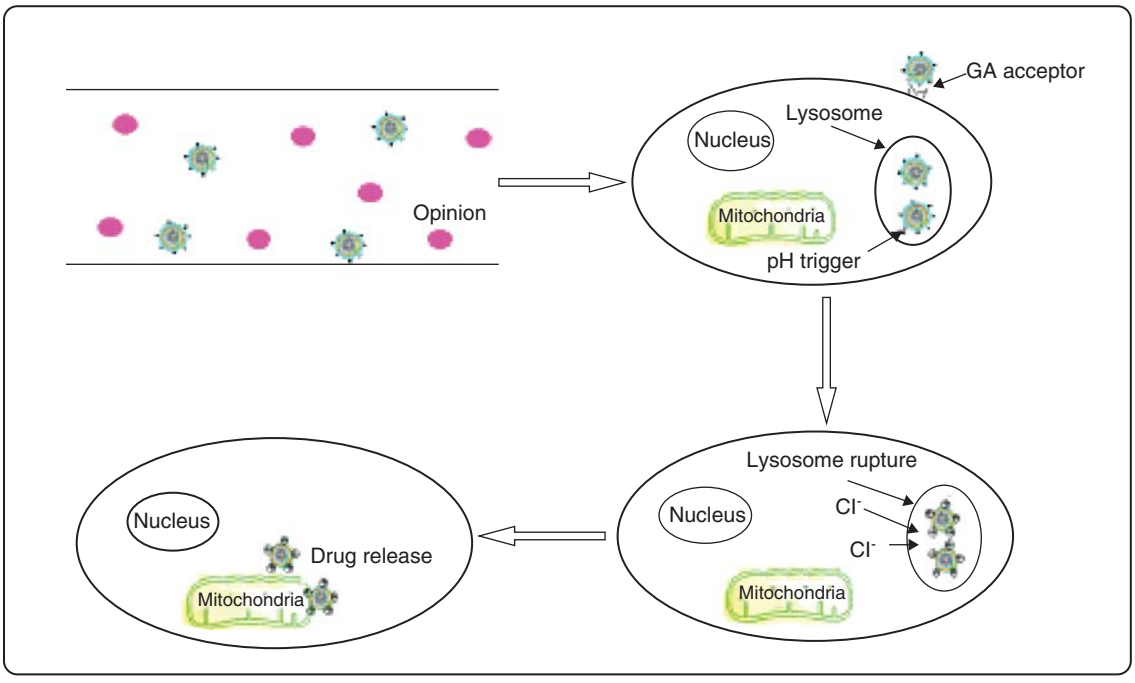

Figure 1. The multi-functional roles of novel materials and their physiological dispositions.

largely taken up by the liver rapidly in the order: TM-rHSA > D494N ≥ A320T = D63N, which is consistent with their degree of mannosylation. *In vivo* experiments suggested that > 90% of the TM-rHSA is taken up by hepatic non-parenchymal cells. To examine which type of hepatic non-parenchymal cells were involved in the hepatic uptake of TM-rHSA, cellular uptake experiments were performed using primary-cultured endothelial cells and KCs. The findings indicated that little uptake of ^{125}I-labeled TM-rHSA was observed in endothelial cells, while KC absorbed TM-rHSA specifically.

Sungeun *et al.* [31] compared the biological properties of neolactosyl human serum albumin (LSA) and neomannosyl human serum albumin (MSA). Both were labeled with ^{99m}Tc [38] and produced as described previously [39,40]. The studies showed that ^{99m}Tc-LSA and ^{99m}Tc-MSA enter the liver through the portal vein and hepatic artery. ^{99m}Tc-LSA is then taken up by hepatocytes, is metabolized and enters the hepatic vein. ^{99m}Tc-MSA is taken up by KCs and endothelial cells and then enters the hepatic vein. ^{99m}Tc-LSA is taken up by hepatocytes and enters the bile duct.

4.2 HSC targeting materials

HSCs play a central role in the progression of liver fibrosis, independent of the etiology of the underlying diseases [41,42]. There are no effective therapies to treat liver fibrosis in patients in whom the causative agent cannot be removed [43]. In recent years, an increasing number of research papers on liver fibrosis showed that it is reversible [44]. Bile duct ligation-induced fibrosis and CCl_4-induced liver fibrosis can be reversed after the withdrawal of the inciting stimulus [45].

In HSC-selective targeting strategies, the receptor expression for some growth factors on the cell surface is drastically upregulated. Examples of receptors that are upregulated on activated cells are the platelet-derived growth factor (PDGF) receptors [46], the mannose-6-phosphate/insulin-like growth factor II (M6P/IGF-II) receptor [47] and many receptors that allow HSCs to interact with the surrounding ECM. Thus, HSCs form an attractive cellular target for the treatment of hepatic fibrogenesis.

In several recent studies, some modified albumins have been used to target drugs to HSCs: losartan, mycophenolic acid [48,49], DOX [50], 15d-prostaglandin J2 [51], gliotoxin [52], the viral vector HVJ [53], pentoxifylline [54], IL-10 [55] and a kinase inhibitor [56]. Most of these constructs displayed antifibrotic effects *in vivo*.

Losartan-M6PHSA was synthesized by Moreno *et al.* [57]. M6PHSA was prepared as follows: HSA was modified with mannose 6 phosphate groups. Briefly, *p*-nitrophenyl-a-D-mannopyranoside was phosphorylated and after reduction of the nitro group it was coupled with HSA. Beljaars *et al.* prepared M6P-modified albumin, which was purified using an Amicon Stirred Cell (Amicon, Danvers, MA, USA) followed by Sephadex G-25 gel chromatography (Pharmacia, Uppsala, Sweden). [33]. The results demonstrated that animals receiving losartan-M6PHSA showed losartan levels that corresponded to 81% of the last injected dose, which was at least 20% of the cumulative dose, while oral losartan

yielded liver tissue levels corresponding to only 4% of the cumulative dose (15% of the last dose administered). These results illustrate the preferential hepatic accumulation of losartan-M6PHSA.

5. Expert opinion

The pathogenesis of liver diseases is complex and often involves a variety of cells. The key factor to improve the drug treatment was the design and synthesis of appropriate polymer materials to target the right cells. This review reveals that important developments have been made in the development of liver-targeting materials that can target hepatic parenchymal or hepatic non-parenchymal cells. From the review, we have learnt that different types of materials with cell-specific targeting have been designed and synthesized. These materials have been widely used in various dosage forms, such as liposomes, nanoparticles, and applied in a variety of therapeutic drugs, including chemicals, plant-based drugs and gene drugs.

Compared with normal preparations, the preparations that are modified by novel materials have shown strong and selective cell targeting *in vivo* and *in vitro*. These novel materials could significantly improve the distribution of drugs in target cells, increase gene transfection efficiency, reduce the side effects and lower cell cytotoxicity.

There has been significant progress in the development of these novel materials in the laboratory, but so far no new materials have been introduced in the clinical setting. One reason for this may be the intravenous route of administration of these novel materials, which restricts the biocompatibility and *in vivo* stability of these new materials. The high R&D costs and the difficulty of large-scale production are other possible reasons. Therefore, the clinical application of these new materials is still a long way away.

The liver-targeted delivery of drugs via a receptor-mediated process can be improved. However, it may not necessarily be effective from a pharmacokinetic point of view. Since the recognition of ligands by the receptors is highly efficient, the carriers could be rapidly delivered to the target cells. Therefore, the concentration–time profile in the target is rapidly switched to the elimination phase, which would result in a short duration of drug exposure. Therefore, it is necessary to control the rate of the receptor–ligand binding. On the other hand, the carriers that are modified by the novel materials could improve the targeting efficiency. However, knowing how to avoid the non-specific binding and the recognition of plasma opsonics, in order to make the carrier reach the target tissue easily are also important aspects.

At present, it is a well-known fact that specific delivery of a drug to target tissues or target cells will dramatically improve its efficacy and reduce side effects. However, despite such efforts, tissue accumulation and cell-specific delivery have resulted in less than expected dramatic improvement in drug action. A possible reason for this shortcoming might be the fact that many drugs act on molecular targets on or inside organelles within the cell. The uptake of the carrier into the cell by endocytosis results in the formation of endosomes; these endosomes then enter the lysosome which contains high concentrations of a variety of hydrolysis enzymes. As a result, the drug is damaged by the hydrolysis enzyme and will not be effective in the target. So, despite successful cell-specific delivery or even cytosolic internalization, drug action may not improve if the drug molecule is unable to interact with its specific subcellular target site. Therefore, it is also important to address the subcellular targeting of a therapeutic molecule in any strategy designed to increase the therapeutic effect. So the studies of new biocompatible materials with multi-functional roles (**Figure 1**), such as lysosome escape function, subcell targeting capabilities, temperature-sensitive function and acid-sensitive function, will form the basis for liver targeting in modern drug delivery approaches.

In terms of formulation design issues for the targeted delivery these novel materials, it is clear that modification of these materials does matter, which, in our opinion, plays an important in its properties such as biocompatibility, safety and tolerability. Therefore, well-designed, comprehensive studies incorporating a complete assessment of tolerability, safety, biocompatibility and multi-functionality of these modified materials must be an integral part of future work. These particulates must be fully characterized such that their characteristics (e.g., size range, surface morphology, composition, molecular weight, pharmacokinetics, tissue distribution) are well understood and documented.

The differential targeting of hepatocytes is necessary for specifically imaging the metabolic and immune functions of the liver, and intracellular receptors, which are translocated into nuclei after binding to ligands, are of special interest. Thus, newly synthesized materials that make use of receptor–ligand interaction will be used more widely. Further research into the use of clinical materials and the design of smart materials for multi-drug delivery to different organelles is important future studies on new materials. It is hoped that these targeted therapeutics will benefit patients with liver disorders in the near future.

Acknowledgement

ZP Chen and L Xiao contributed equally to the project and are considered co-first authors.

Declaration of interest

This work was financially supported by the National Natural Science Foundation of China (81102814), the Science Foundation of Nanjing University of Chinese Medicine (09XZR16) and the Point Development of Nanjing University of Chinese Medicine (10XPY03). The authors state no conflict of interest.

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