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***Corresponding author:** Swarupananda Mukherjee, Department of Pharmacy, NSHM Knowledge Campus, Kolkata, Group of Institutions, 124 B.L.Saha Road, Kolkata - 700053, West Bengal, India, Tel: +91-905116425; Email: swarup_mukherjee@rediffmail.com, swarupananda.mukherjee@nshm.com

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Mini Review

Lipid nanoparticulate drug delivery system for the treatment of hepatic fibrosis

Swarupananda Mukherjee^{1*}, Ayon Dutta² and Dipanjana Ash³

¹Assistant Professor, Department of Pharmacy, NSHM Knowledge Campus, Kolkata - Group of Institutions, 124 B.L.Saha Road, Kolkata- 700053, West Bengal, India

²Assistant Professor, Department of Pharmaceutical Technology, Bengal School of Technology (A College of Pharmacy), Delhi Road, Sugandha, Hoogly, Pin-712102, West Bengal, India

³Assistant Professor, Department of Pharmaceutics, BCDA College of Pharmacy and Technology, 78/1 Jessore Road (S), Hridaypur, Barasat, Kolkata-700127, West Bengal, India

Abstract

Background: Irreversible hepatic fibrosis, an excessive production and accumulation of extra cellular matrix by hepatic stellate cells in the liver, becomes a remarkable economic burden in global health care system. Low therapeutic efficacy and undesirable systemic effect of conventional therapies limit their clinical applications to target hepatic stellate cells.

Method: Surface engineered lipid nano-particle becomes a potential candidate to deliver anti-fibrotic nutrients or Small interfering RNA (siRNA) of fibrogenic genes for treating hepatic disorders.

Conclusion: This mini review focuses on different strategies of surface engineered organic lipid nanoparticles for the treatment of hepatic fibrosis by targeting specific and un-specific Hepatic Stellate Cells (HSCs).

Abbreviations

CXCR4: Chemokines Receptor Type 4; ECM: Extra Cellular Matrix; HA: Hyaluronic Acid; HSCs: Hepatic Stellate Cells; IFN- α -1b: Interferon- α -1b; M6P/IGF II: Mannose-6- Phosphate/ insulin-Like Growth Factor II; PDGF- β : Platelet-Derived Growth Factor Receptor; RBP: Retinol Binding Protein; siRNA: small interfering RNA; TGF- β 1: Transforming Growth Factor- β 1

Introduction

In 21st century Hepatic disorders such as hepatitis, hepatic fibrosis, cirrhosis, and hepatocellular carcinoma, the considerable economical burden on global healthcare infrastructure, accounts for 5-10% of total mortality in the world per year due to restricted treatment option. Hepatic fibrosis is the excessive accumulation of Extra Cellular Matrix

(ECM) protein including collagen in the liver attributed to the trans-differentiation of HSC by fibrogenic cytokines such as Transforming Growth Factor- β 1 (TGF- β 1), angiotensin II, and leptin and ultimately resulting in the further development of cirrhosis, liver failure and portal hypertension due to deformation of hepatic architecture and evolution of regenerating hepatocytes nodules. Hepatitis C, alcohol abuse and non-alcoholic steatohepatitis have been recognized as a major cause of irreversible hepatic fibrosis. Therefore, HSC becomes a cellular target for the treatment of hepatic fibrosis [1]. Low therapeutic efficacy and undesirable systemic effect of standard conventional therapies limit their clinical applications in this field. Nano-material based drug delivery systems such as Lipid, polymeric, inorganic and protein nanoparticles have been shown an exceptional potential for novel therapeutic approaches to deliver anti-fibrotic nutrients



or siRNA of fibrogenic genes for treating hepatic disorders [2]. Their ease of surface modification, encapsulation efficiency, bio-compatibility, bio-degradability, physico-chemical stability, feasibility in scaling up and target specificity offer great advantages [3]. This mini review focuses on surface engineering of organic lipid nanoparticles for the treatment of hepatic fibrosis via specific and un-specific HSC-targeting.

Methodology, selection criteria, inclusion and exclusion criteria for the preparation of HSC targeted surface engineered organic lipid nanoparticles.

Surface engineered lipid nanoparticles either actively or passively target trans-differentiated HSC through various cell surface receptors, such as Retinol-binding protein (RBP), Mannose-6-phosphate/insulin-like growth factor II (M6P/

IGF II), Platelet-derived growth factor receptor (PDGF- β), Hyaluronic acid (HA), Chemokines receptor type 4 (CXCR4) and galactosyl receptor conjugated with several ligands like cRGD* peptide, C*SRNLIDC* peptide, M6P, cyclic C*SRNLIDC* peptide, RBP via direct coating or grafting (Table 1) [2,4].

Biocompatible and bio-degradable surface engineered lipid nano carrier should have sufficient internalization capacity by HSC, entrapment efficiency, penetrating power to interact with HSC for the treatment of hepatic fibrosis. However, the delivery of drug and gene through lipid-based nano carrier is limited by intrinsic and biological barriers [2,4]. Table 2 summarizes ligand-based lipid nanoparticulate approaches for targeting HSC.

Conclusion and Future prospects

Surface engineered lipid nanoparticles with various targeting ligands on the surface of HSCs become potent candidates for the treatment of hepatic fibrosis. Their higher biocompatibility, biodegradability and lower immunogenicity, toxicity compared to inorganic nanoparticles offer great advantages. ONPATPRO, the first FDA approved HSC-targeting lipid nano-particle, showed remarkable pharmacological effects by crossing hepatic barrier. Although HSC targeting has been challenging, the low quantity of surface engineered lipid nano-particles demonstrated significant therapeutic efficacy in clinical trials.

Table 1: Methodology for the preparation of surface engineered lipid nanoparticulate DDS.

Ligand	Lipid nano carrier	Methodology	Reference
Vitamin A	Lipid nano particles	Direct mixing	[5]
Vitamin A	Liposome	Direct mixing	[6,7]
C*SRNLIDC*	Lipid nanoparticles	Grafting of cyclic peptides on phospholipids	[2,8]
cRGD* peptide	Sterically stable Liposome	Grafting of sulfhydryl group at the cysteine residue to a liposome	[9]
M6P-HSA	Neoglycoprotein-based nanoparticles	Desolvation	[2]

Table 2: Different formulation strategies of surface engineered lipid nanoparticles.

Formulation	Ligand	Targeted receptor	Delivered drug	Remarks	Reference
Liposome	C*SRNLIDC*	PDGF- β	siRNA and Heat shock protein 47-siRNA	Remarkable gene silencing efficacy (37%), anti-fibrotic effects was observed. In-vivo and in-vitro study on mouse showed significant extent of internalization by HSCs and 2.37 fold higher liver uptake respectively compare to non-targeted liposomes	[7,8]
Sterically stable Liposome	cRGD* peptide	Type VI Collagen	IFN- α -1b	Significant (10-fold) increased intracellular delivery of the drug to HSCs was observed in bile duct ligation induced hepatic fibrosis in Wistar rats than non-targeted liposomes.	[9,10]
Fluorescein isothiocyanate-conjugated Liposome	cRGD* peptide	Type VI Collagen	Oxymatrine	There was notable down regulation of fibrosis-associated biomarkers along with increased delivery of drug to HSCs in CCl ₄ -induced fibrosis in rats. In-vitro study revealed inhibited cell viability and induced apoptosis of HSCs.	[4,11,12]
Liposome	Vitamin A	RBP	a. siRNA b. Rho-kinase inhibitor Y-27632	a. The expression of procollagen 1 was reduced in mice with hepatic fibrosis by prolonging survival. b. Conjugated liposome revealed 100 fold more effectiveness to inhibit HSC activation than un-conjugated liposome.	[6,13,14]
Liposome	M6P-HSA	M6P	Sendai virus containing plasmid DNA	Efficient selective targeting of HSCs in mice was observed.	[15]
Niosomal nano-vesicles	Vitamin A and anti-platelet-derived growth factor receptor antibody	RBP and PDGF- β	Silibinin, iFluor [®] 790 acid	Antibody-conjugated nano-vesicles showed increased Silibinin uptake (4 fold) in liver of mice at 2 h after dosing compare to unconjugated niosomes.	[16,17]

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