ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2024 November 7; 30(41): 4411-4517

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 30 Number 41 November 7, 2024

EDITORIAL

4411 Navigating new horizons in inflammatory bowel disease: Integrative approaches and innovations

Zhang SY

REVIEW

4417 Trypsin in pancreatitis: The culprit, a mediator, or epiphenomenon?

Gukovskaya AS, Lerch MM, Mayerle J, Sendler M, Ji B, Saluja AK, Gorelick FS, Gukovsky I

ORIGINAL ARTICLE

Retrospective Study

4439 Clinical application of oral contrast-enhanced ultrasound in evaluating the preoperative T staging of gastric cancer

Liang Y, Jing WY, Song J, Wei QX, Cai ZQ, Li J, Wu P, Wang D, Ma Y

Basic Study

4449 Amino acid deletions at positions 893 and 894 of cytotoxin-associated gene A protein affect *Helicobacter pylori* gastric epithelial cell interactions

Xue ZJ, Gong YN, He LH, Sun L, You YH, Fan DJ, Zhang MJ, Yan XM, Zhang JZ

SCIENTOMETRICS

4461 Mapping the evolution of liver aging research: A bibliometric analysis

Han QH, Huang SM, Wu SS, Luo SS, Lou ZY, Li H, Yang YM, Zhang Q, Shao JM, Zhu LJ

LETTER TO THE EDITOR

4481 Albumin-bilirubin score in non-malignant liver and other diseases

Zhang LF, Chen LX, Yang WJ, Hu B

4484 Addressing diagnostic delays in inflammatory bowel diseases in Germany

Zhang SY, Lin Y

4490 Abnormally activated wingless/integrated signaling modulates tumor-associated macrophage polarization and potentially promotes hepatocarcinoma cell growth

Wang WL, Tam PKH, Chen Y

4496 Harnessing the power of *Calculus bovis*: Anti-cancer properties and Wnt pathway modulation in hepatocellular carcinoma

Goyal H, Parwani S, Fatima K, Kaur J

4503 MicroRNA-206 as a promising epigenetic approach to modulate tumor-associated macrophages in hepatocellular carcinoma

Ramoni D, Montecucco F

4509 Encapsulating taurine into liposomes: A promising therapeutic for liver fibrosis

Zhang XJ, Jiang XY, Ma YL, Huang FY, Huang ZW

4514 Contribution of gut microbiota to the development of Crohn's disease: Insights gained from fecal microbiota transplantation studies in mice

Wang J, Meng Y, Guo ZG

Contents

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Naoki Asano, MD, PhD, Professor, Division of Carcinogenesis and Senescence Biology, Tohoku University Graduate School of Medicine; Division of Cancer Stem Cell, Miyagi Cancer Center Research Institute, Natori 981-1293, Miyagi, Japan. asanon@med.tohoku.ac.jp

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJG* as 4.3; Quartile: Q1. The *WJG*'s CiteScore for 2023 is 7.8.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Hua-Ge Yu*; **Production Department Director:** *Xu Guo*; **Cover Editor:** *Jia-Ru Fan.*

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF
Jian-Gao Fan (Chronic Liver Disease)

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
November 7, 2024

COPYRIGHT
© 2024 Baishideng Publishing Group Inc

PUBLISHING PARTNER
Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

POLICY OF CO-AUTHORS
https://www.wjgnet.com/bpg/GerInfo/310

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
https://www.shca.org.cn
https://www.zs-hospital.sh.cn

E-mail: office@baishideng.com https://www.wjgnet.com

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2024 November 7; 30(41): 4509-4513

DOI: 10.3748/wjg.v30.i41.4509

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTER TO THE EDITOR

Encapsulating taurine into liposomes: A promising therapeutic for liver fibrosis

Xue-Juan Zhang, Xiao-Yi Jiang, Yi-Lin Ma, Fei-Yi Huang, Zheng-Wei Huang

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Mahmoud MZ

Received: August 17, 2024
Revised: September 24, 2024
Accepted: October 8, 2024
Published online: November 7, 2024
Processing time: 66 Days and 13.7 Hours

Xue-Juan Zhang, Xiao-Yi Jiang, Yi-Lin Ma, Fei-Yi Huang, Zheng-Wei Huang, College of Pharmacy, Jinan University, Guangzhou 511443, Guangdong Province, China

Corresponding author: Zheng-Wei Huang, PhD, Associate Professor, College of Pharmacy, Jinan University, No. 855 East Xingye Dadao, Panyu District, Guangzhou 511443, Guangdong Province, China. huangzhengw@jnu.edu.cn

Abstract

We summarize the mechanism by which taurine (Tau) inhibits autophagy and induces iron apoptosis in hepatic stellate cells. Tau interacts with autophagy regulates multifunctional proteins, microtubule-associated protein 1 light chain 3 Beta, and autophagy-related gene 5 to inhibit autophagy, binds to ferritin heavy chain 1 and nuclear receptor coactivator 4 to trigger ferritin autophagy, and interacts with glutathione peroxidase 4 to promote iron apoptosis. There is a solid rationale for developing Tau-based therapies targeting autophagy and ferroptosis regulation. From a pharmaceutical point of view, there are certain requirements for Tau protein delivery systems, such as loading efficiency, stability, and targeting. Nanomaterials should also contain a hydrophilic motif similar to Tau to optimize loading efficiency. Since Tau is a hydrophilic molecule with high water solubility, liposomes, micelles, and amphiphilic polymer nanoparticles may represent a superior choice. The nanostructure of the liposome includes a water region and a lipid membrane to sequester hydrophilic and hydrophobic drugs, respectively, whereas Tau is expected to be loaded into the water region. In addition, a representative method of actively targeting hematopoietic stem cells is introduced. A Tau-based method for the treatment of liver fibrosis is proposed based on the formulation of common liposomes (lecithin plus cholesterol).

Key Words: Taurin; Liposome; Liver fibrosis; Targeted therapy; Nanoparticle delivery systems; Hepatic stellate cells

Core Tip: Nanoparticle delivery systems are effective for delivering taurine (Tau). The nanoarchitecture of liposomes includes a water zone and a lipid membrane to accommodate hydrophilic and hydrophobic drugs, respectively. Tau is a hydrophilic molecule with high water solubility, and it is expected to be loaded into the water zone. In theory, hepatic stellate cells (HSCs) may be targeted by Tau-incorporated liposomes *via* two mechanisms: Passive targeting and active targeting. Active targeting is more robust as it takes advantage of the unique features of the lesion site. Based on a formulation for common liposomes (lecithin plus cholesterol), Tau-based therapeutics was proposed to treat liver fibrosis as follows: A targetable liposome was fabricated through the combination of common lecithin and cholesterol, along with modified lecithin or cholesterol with HSC targetability. Tau was dispersed into the water zone of this liposomal system.

Citation: Zhang XJ, Jiang XY, Ma YL, Huang FY, Huang ZW. Encapsulating taurine into liposomes: A promising therapeutic for liver fibrosis. *World J Gastroenterol* 2024; 30(41): 4509-4513
URL: https://www.wjgnet.com/1007-9327/full/v30/i41/4509.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i41.4509

TO THE EDITOR

We are pleased to provide a critique of the research article, which was published in the *World Journal of Gastroenterology* [1]. The authors describe the use of taurine (Tau) as a bioactive compound to inhibit autophagy and activate the ferroptosis pathway in hepatic stellate cells (HSCs) as a potential therapy for liver fibrosis. The effect of Tau on attenuating the extracellular matrix in liver fibrosis was confirmed. A series of biochemical and pharmacological tests were performed to assess the hallmarks of autophagy [*e.g.*, microtubule-associated protein 1 light chain 3 beta (LC3B), Beclin 1, and autophagy regulates multifunctional proteins (p62)] and ferroptosis (*e.g.*, reactive oxygen species, glutathione, and malondialdehyde). A pioneer molecular docking experiment between Tau and ferritin heavy chain 1 (FTH1) or nuclear receptor coactivator 4 (NCOA4) was performed to demonstrate the presence of ferritinophagy, which represents crosstalk between autophagy and ferroptosis.

The article summarizes autophagy inhibition and ferroptosis induction mechanisms of Tau in HSCs, as shown in Figure 1. Briefly, Tau interacts with p62, LC3B, and autophagy-related gene 5 to inhibit autophagy, binds to FTH1 and NCOA4 to trigger ferritinophagy, and interacts with glutathione peroxidase 4 to promote ferroptosis.

In addition to this article, similar results were reported in other studies. It was well documented that Tau regulates cellular autophagy[2] and ferroptosis[3] caused by various factors. This suggests that developing Tau-based therapeutics based on autophagy and ferroptosis regulation is on a relatively firm ground.

Nevertheless, there is still a long journey toward the real-world application of Tau-based therapeutics for liver fibrosis. The major pending issue that must be addressed is the design of an appropriate delivery system for Tau. From the perspective of pharmaceutics, an ideal Tau delivery system should have satisfactory loading efficiency, stability, and targetability. The molecular data for Tau, which was not provided in the original article, should be examined to design such a system. Based on the online molecule database (*e.g.*, molinspiration cheminformatics, https://www.molinspiration.com/) and the literature[4,5], the molecular information for Tau is summarized in Figure 2.

The delivery systems that are suitable for Tau must be considered, which are based on the information shown in Figure 2. To ensure loading efficiency, stability, and targetability, nanoparticle delivery systems (NDS) are appropriate choices, as they have been extensively reported to exhibit these properties[6]. As shown in Figure 2, the chemical stability of Tau is relatively high. Thus, NDS design considerations to improve stability may be partially exempt. However, it is advisable to avoid NDS with unsatisfactory stability, such as nanocrystals[7], exosomes[8], and DNA origamis[9]. Furthermore, Tau is a hydrophilic molecule with a high water solubility. Based on the rationale of "like dissolves like", the nanomaterial should contain motifs with similar hydrophilicity as Tau to ensure an acceptable loading efficiency. NDS is primarily composed of hydrophobic nanomaterials, such as solid lipid nanoparticles and nanostructured lipid carriers, which are less likely to achieve this goal. From this perspective, liposomes[10], micelles, and polymeric nanoparticles with amphiphilic properties (containing both hydrophilic and hydrophobic blocks) may be considered as better alternatives. Because liposomes are biocompatible vehicles with clinical translation potential as evidenced by the licensed products (Doxil, Arikayce, *etc.*), they stand out as most promising candidates for the Tau delivery system. The liposome nanoarchitecture involves a water zone and a lipid membrane to accommodate hydrophilic and hydrophobic drugs, respectively, and Tau is expected to be loaded into the water zone.

The targetability consideration has not been fulfilled. As demonstrated in the original article, HSCs are prime targets for liver fibrosis, and targeted therapy toward HSCs is emphasized herein. In theory, two processes: (1) Passive targeting and (2) Active targeting, are developed to target HSCs by Tau-incorporated liposomes. Passive targeting refers to taking advantage of the liver sinusoidal fenestrae diameter and rendering a < 100 nm particle size for the liposomes. For active targeting, the ligands of the abundantly expressed receptors on HSCs, including collagen type VI receptor, mannose 6-phosphate receptor, platelet-derived growth factor receptor-β, and retinol-binding protein, are tagged onto the liposome surface[11]. Active targeting is considered more robust as it takes advantage of the unique features of the lesion site while employing size-dependent passive targeting resulting in the accumulation at other sites with similar size-dependent endocytosis tendencies. For example, given the same < 100 nm particle size for the passive targeting of HSCs, this size condition may also be used for lymph node[12] targeting and enhanced permeability and retention effect-based tumor

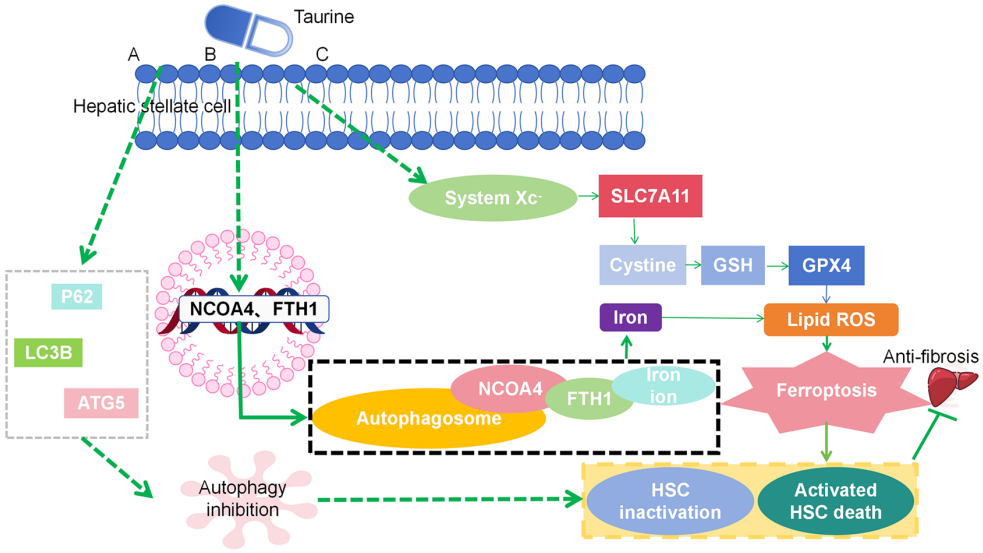

Figure 1 Autophagy inhibition and ferroptosis induction mechanisms of taurine in hepatic stellate cells.

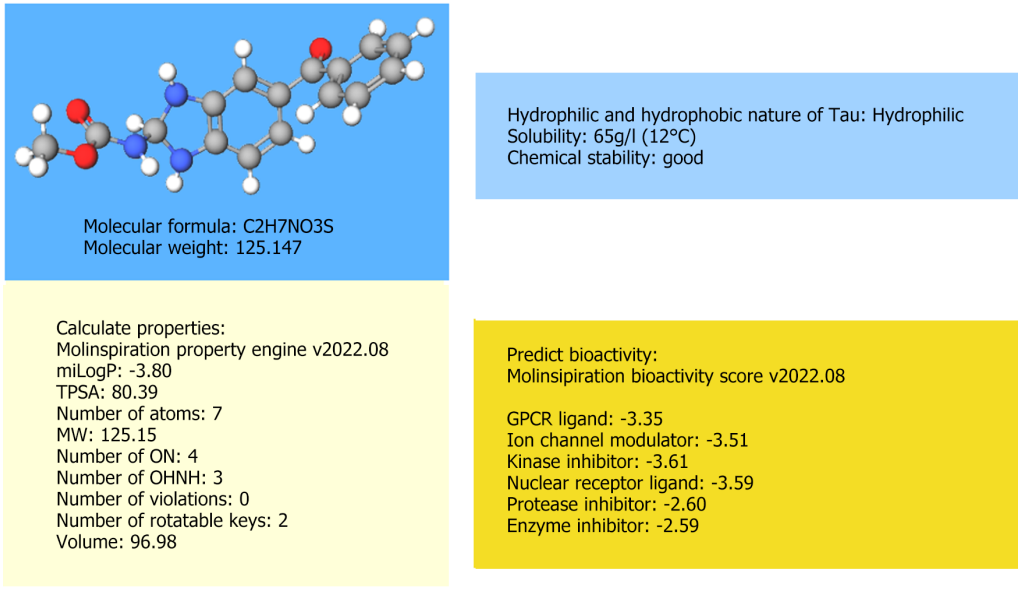

Figure 2 Molecular information for taurine collected.

targeting[13]. In the liver, liposomes < 100 nm in size can also impact normal hepatocytes adjacent to HSCs[14]. This may lead to unexpected toxicity issues; therefore, we recommend adopting active targeting strategies.

The representative modification methods for the active targeting of HSCs are presented herein[1]. The cyclic Arg-Gly-Asp (cRGD) peptide can be employed to target the collagen type VI receptor[15]. Mannose 6-phosphate human serum albumin (M6P-HSA) can be used to target the mannose 6-phosphate receptor[16]. The cyclic peptide cysteine-serine-arginine-asparagine-leucine-isoleucine-aspartic acid-cysteine (CSRNLIDC), which has high selectivity, may be used to target the platelet-derived growth factor receptor-β[17]. Vitamin A is an ideal ligand to target retinol-binding protein[18]. Through click chemistry techniques, these ligands can be covalently bound with lecithin or cholesterol, which are the major components of liposomes[18]. Subsequently, the targeting liposomes can be produced by thin-film hydration, solvent evaporation, or other standard methods.

Based on the formulation of common liposomes (lecithin plus cholesterol), Tau-based therapeutics to treat liver fibrosis were proposed as follows: A targetable liposome was fabricated by combining lecithin and cholesterol, along with modified lecithin or cholesterol with HSCs targetability (*i.e.*, cRGD, M6P-HSA, CSRNLIDC, and vitamin A decorated ones). Tau was dispersed into the water zone of this liposomal system. A schematic illustration of this process is shown in Figure 3. We advocate for the science community to validate the feasibility of the above design.

It is expected that this work could provide insight into the design and development of Tau-based therapeutics for liver fibrosis management and increase our understanding of liver fibrosis-targeting vehicles. We are optimistic that relevant studies or Tau-encapsulated vehicles products will be available in the near future.

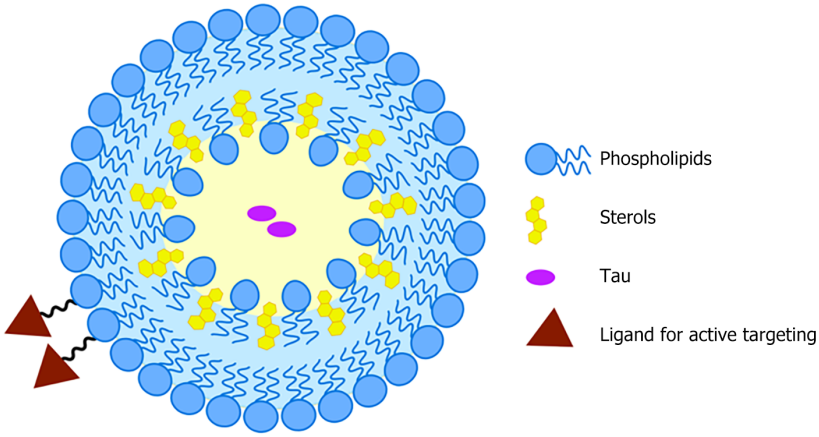

Figure 3 Schematic illustration of taurine-embedded targeting liposomes.

FOOTNOTES

Author contributions: Zhang XJ contributed to manuscript writing and file sorting; Jiang XY contributed to core tip writing and Figure 2 making; Ma YL contributed to abstract writing and Figure 1 making; Huang FY contributed to Figure 3 making; Huang ZW contributed to theoretical framework, supervision, proofreading, and submission.

Supported by the National Natural Science Foundation of China, No. 82373800; Guangdong Basic and Applied Basic Research Foundation, No. 2024A1515011236; and General Program of Administration of Traditional Chinese Medicine of Guangdong Province, No. 20241071.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country of origin: China

ORCID number: Zheng-Wei Huang 0000-0003-2351-7347.

S-Editor: Fan M
L-Editor: A
P-Editor: Chen YX

REFERENCES

1 **Li S**, Ren QJ, Xie CH, Cui Y, Xu LT, Wang YD, Li S, Liang XQ, Wen B, Liang MK, Zhao XF. Taurine attenuates activation of hepatic stellate cells by inhibiting autophagy and inducing ferroptosis. *World J Gastroenterol* 2024; **30**: 2143-2154 [PMID: 38681990 DOI: 10.3748/wjg.v30.i15.2143]

2 **Sun Y**, Dai S, Tao J, Li Y, He Z, Liu Q, Zhao J, Deng Y, Kang J, Zhang X, Yang S, Liu Y. Taurine suppresses ROS-dependent autophagy *via* activating Akt/mTOR signaling pathway in calcium oxalate crystals-induced renal tubular epithelial cell injury. *Aging (Albany NY)* 2020; **12**: 17353-17366 [PMID: 32931452 DOI: 10.18632/aging.103730]

3 **Zhang X**, Zhao L, Ying K, Xu J, Huang Y, Zhu R, Ding Y, Cai W, Wu X, Miao D, Xu Q, Zeng Y, Yu F. TUG1 protects against ferroptosis of hepatic stellate cells by upregulating PDK4-mediated glycolysis. *Chem Biol Interact* 2023; **383**: 110673 [PMID: 37582412 DOI: 10.1016/j.cbi.2023.110673]

4 **Wu D**, Song L, Zhu C, Zhang X, Guo H, Yang C. Solubility of taurine and its application for the crystallization process improvement. *J Mol Liq* 2017; **241**: 326-333 [DOI: 10.1016/j.molliq.2017.06.043]

5 **Saidi B**, Warthesen J. Analysis and Heat Stability of Taurine in Milk. *J Dairy Sci* 1990; **73**: 1700-1706 [DOI: 10.3168/jds.s0022-0302(90)78846-7]

6 **Oh JY**, Yang G, Choi E, Ryu JH. Mesoporous silica nanoparticle-supported nanocarriers with enhanced drug loading, encapsulation stability, and targeting efficiency. *Biomater Sci* 2022; **10**: 1448-1455 [PMID: 35229845 DOI: 10.1039/d2bm00010e]

7 **Li J**, Wang Z, Zhang H, Gao J, Zheng A. Progress in the development of stabilization strategies for nanocrystal preparations. *Drug Deliv* 2021; **28**: 19-36 [PMID: 33336609 DOI: 10.1080/10717544.2020.1856224]

8 **Gao Y**, Yuan Z, Yuan X, Wan Z, Yu Y, Zhan Q, Zhao Y, Han J, Huang J, Xiong C, Cai Q. Bioinspired porous microspheres for sustained hypoxic exosomes release and vascularized bone regeneration. *Bioact Mater* 2022; **14**: 377-388 [PMID: 35386817 DOI: 10.1016/j.bioactmat.2022.01.041]

9 **Khoshouei A**, Kempf G, Mykhailiuk V, Griessing JM, Honemann MN, Kater L, Cavadini S, Dietz H. Designing Rigid DNA Origami Templates for Molecular Visualization Using Cryo-EM. *Nano Lett* 2024; **24**: 5031-5038 [PMID: 38602296 DOI: 10.1021/acs.nanolett.4c00915]

10 **Nsairat H**, Ibrahim AA, Jaber AM, Abdelghany S, Atwan R, Shalan N, Abdelnabi H, Odeh F, El-Tanani M, Alshaer W. Liposome bilayer stability: emphasis on cholesterol and its alternatives. *J Liposome Res* 2024; **34**: 178-202 [PMID: 37378553 DOI: 10.1080/08982104.2023.2226216]

11 **Böttger R**, Pauli G, Chao PH, Al Fayez N, Hohenwarter L, Li SD. Lipid-based nanoparticle technologies for liver targeting. *Adv Drug Deliv Rev* 2020; **154-155**: 79-101 [PMID: 32574575 DOI: 10.1016/j.addr.2020.06.017]

12 **Mao Y**, Liu J, Shi T, Chen G, Wang S. A Novel Self-Assembly Nanocrystal as Lymph Node-Targeting Delivery System: Higher Activity of Lymph Node Targeting and Longer Efficacy Against Lymphatic Metastasis. *AAPS PharmSciTech* 2019; **20**: 292 [PMID: 31428888 DOI: 10.1208/s12249-019-1447-3]

13 **Sharifi M**, Cho WC, Ansariesfahani A, Tarharoudi R, Malekisarvar H, Sari S, Bloukh SH, Edis Z, Amin M, Gleghorn JP, Hagen TLMT, Falahati M. An Updated Review on EPR-Based Solid Tumor Targeting Nanocarriers for Cancer Treatment. *Cancers (Basel)* 2022; **14** [PMID: 35740534 DOI: 10.3390/cancers14122868]

14 **Giraudi PJ**, Becerra VJ, Marin V, Chavez-Tapia NC, Tiribelli C, Rosso N. The importance of the interaction between hepatocyte and hepatic stellate cells in fibrogenesis induced by fatty accumulation. *Exp Mol Pathol* 2015; **98**: 85-92 [PMID: 25533546 DOI: 10.1016/j.yexmp.2014.12.006]

15 **Beljaars L**, Molema G, Schuppan D, Geerts A, De Bleser PJ, Weert B, Meijer DK, Poelstra K. Successful targeting to rat hepatic stellate cells using albumin modified with cyclic peptides that recognize the collagen type VI receptor. *J Biol Chem* 2000; **275**: 12743-12751 [PMID: 10777570 DOI: 10.1074/jbc.275.17.12743]

16 **Adrian JE**, Kamps JA, Poelstra K, Scherphof GL, Meijer DK, Kaneda Y. Delivery of viral vectors to hepatic stellate cells in fibrotic livers using HVJ envelopes fused with targeted liposomes. *J Drug Target* 2007; **15**: 75-82 [PMID: 17365276 DOI: 10.1080/10611860601141481]

17 **Jia Z**, Gong Y, Pi Y, Liu X, Gao L, Kang L, Wang J, Yang F, Tang J, Lu W, Li Q, Zhang W, Yan Z, Yu L. pPB Peptide-Mediated siRNA-Loaded Stable Nucleic Acid Lipid Nanoparticles on Targeting Therapy of Hepatic Fibrosis. *Mol Pharm* 2018; **15**: 53-62 [PMID: 29148802 DOI: 10.1021/acs.molpharmaceut.7b00709]

18 **Sato Y**, Murase K, Kato J, Kobune M, Sato T, Kawano Y, Takimoto R, Takada K, Miyanishi K, Matsunaga T, Takayama T, Niitsu Y. Resolution of liver cirrhosis using vitamin A-coupled liposomes to deliver siRNA against a collagen-specific chaperone. *Nat Biotechnol* 2008; **26**: 431-442 [PMID: 18376398 DOI: 10.1038/nbt1396]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com