ISSN 2618-1584 Vol. 4, Issue 8: 15-18, DOI: 10.25236/FMSR.2022.040804

Study on Chitosan Nanoparticles in Liver Cancer

Zhi Zhang[1], Zebin Zhang[2], Xinxin Wang[3], Yulong Li[1,*]

[1]Institute of Problem Solving, Shaanxi University of Chinese Medicine, Xianyang, China
[2]Shaanxi University of Chinese Medicine, Xianyang, China
[3]Northwest University, Xi'an, China
**Corresponding author*

Abstract: *Liver cancer is one of the most common clinical malignant tumors, but the existing conventional chemotherapy drugs have low bioavailability, poor targeting, while killing cancer cells but also hurt the normal cells of the body, will seriously damage the body's immune system. Nanoparticles are used as drugs, protein, vaccines, nucleic acid fragments and other ideal carriers, widely used in biomedical research and clinical diagnosis and treatment, especially in the treatment of tumors, showing great application prospects. Polysaccharides are the polymer of monosaccharides. As natural biological materials, they are not only highly stable, hydrophilic, safe and non-toxic, but also easy to degrade in vivo. They are the most ideal material for the matrix carrier of nano-drug carrying system. In addition, because chitosan has good biocompatibility and no immunogenic properties on this basis, this paper studies the connection, influence and significance between chitosan nanoparticles and liver cancer based on the improvement of chitosan nanoparticles and the direction of targeted therapy.*

Keywords: *Liver cancer; chitosan; nanoparticles; targeted therapy; bioavailability; drugs*

1. Introduction

Liver cancer is one of the most common clinical malignancies, and its mortality rate ranks in the third place among digestive malignancies. To find a carrier that can improve the utilization rate of traditional drugs and target it will have a breakthrough significance for the treatment of HCC. Chitosan good biocompatibility, biodegradable, non-toxic, immune-free characteristics, and is widely used in controlled drug release, tissue scaffold, gene therapy and other research fields. Nanocarriers have large drug load and can also increase the permeability of drugs to biofilms, which is conducive to the efficacy of drugs in cells [1]. As a new drug controlled release system, nano-drug carrying system has become a very shining highlight in the research and development of new drugs. Nanoparticles ultra micro volume, larger than the surface, can smoothly through the human capillaries, conducive to transdermal absorption and intracellular efficacy; swallowed by mononuclear phagocytic system, can quickly distributed in the target parts through the mesh endothelial system; due to the carrier material, can prevent drug degradation by gastric acid, improve the bioavailability of nanoparticles on the target organs, due to the different characteristics of the carrier, slow release effect, high efficiency and low toxic [2].

2. Causes of liver cancer

An increased incidence of hepatocellular carcinoma has been reported in the US, but the cause remains unknown. HCV infection accounts for the majority of the increase in primary HCC cases, and the incidence of primary HCC associated with alcoholic cirrhosis and hepatitis B virus infection remains stable with [3]. Thus, it can be found that in the three early diseases of transformation to HCC, the conversion rate of HCV infection is the main factor. The pathogenic factors of liver cancer are mainly summarized as genetic factors and environmental factors, and a large number of studies confirm that genetic factors are important factors in liver cancer development. Study confirmed the related genes are closely related to all aspects of liver cancer, so that genetic factors have a great role in the impact on liver cancer. In addition, environmental factors are also closely related to the induction and influence of liver cancer, including hepatitis B virus (HBV) infection, tobacco, alcohol, aflatoxin infection, dietary habits, personality, and mental trauma history and many other factors. Smoked food, alcohol and history of liver disease are risk factors for primary hepatocellular carcinoma [4]. This study also proves that environmental factors cannot be ignored in the development of liver cancer.

ISSN 2618-1584 Vol. 4, Issue 8: 15-18, DOI: 10.25236/FMSR.2022.040804

3. Preparation of chitosan nanoparticles

Biotherapy is the only known treatment to completely eliminate cancer cells [5]. Due to the structural characteristics of chitosan and the properties the drug itself, the preparation of chitosan nanoparticles includes ion cross-linking, precipitation, phacoemulsification, reverse phase microemulsion, electrospinning, reverse phase suspension cross-linking, reverse phase evaporation-short-time ultrasonic, reducing amination and so on. In addition, the characterization of chitosan nanoparticles produced by surface charge, particle size distribution, chemical structure, Weis wetting and microstructure imaging. Therefore, we can draw a conclusion that if we want to use biological gene therapy and combine targeted administration to treat liver cancer, one or more methods of producing chitosan nanoparticles should first be selected to solve the problem of basic carrier.

4. Chitosan nanoparticles and liver cancer

Chitosan nanoparticles are used in the field of drug therapy, for the loading of genes, proteins, cytokines, for improving and maintaining cell activity and function and inhibiting apoptosis, for artificial liver as scaffold to promote liver cell attachment, and for liver tumor therapy. Modification of chitosan nanoparticle surface, gene and chitosan nanocomplexes, with more targeted selectivity, may be a future trend in pharmaceutical research. Liver tumor chemotherapy targeting is poor, chitosan nanoparticles will selectively distribute drugs in the tumor site, reduce toxic and side effects, improve the efficacy, will be the hot spot of liver tumor drug research [6].

4.1. Galactosylated chitosan nanoparticles and liver cancer

Large molecular weights of chitosan are less water-soluble and can significantly change the physicochemical properties of chitosan by linking different small molecules to the amino groups of chitosan molecules. Connecting the upper galactose group significantly increases the water-soluble of chitosan. On the surface of hepatocyte membranes [7], there is a large amount of the dessialic acid (ASGR) receptor [8], which can bind to galactose groups to attach chitosan molecules to the surface of hepatocytes through specific binding between receptors / ligands. Therefore, galactosyllated chitosan can be specifically targeted to the liver. GC DNA nanoparticles coated with them resist the degradation of DNA degrading enzyme (DNAaseI) and protect the target gene segment [9], so as to realize the effective transduction of therapeutic genes in vivo, which has certain potential application value in the gene therapy of liver cancer. Chitosan molecules have good biocompatibility and can be improved by different glycosylation modification with different organ targeting, as a non-viral transgenic vector. By injecting nanoparticles with specific therapeutic gene fragments into the human body, the circulating nanoparticles have ligands that specifically bind to the surface receptor of hepatocyte membranes to be swallowed by hepatocytes and play the role of gene therapy.

4.2. Carboxypropyl chitosan nanoparticles and liver cancer

Liver-targeted chitosan-based nano-drug carrying system is a non-viral transgenic vector, which avoids the immune response, viral wild-type mutation and carcinogenic effect caused by viral vector. Tumor cells have more negative charge than normal cell surface, chitosan selectively adsorbs tumor cells in acidic environment and plays an electrical neutralization role, which can directly inhibit tumor cells, inhibit tumor cell activity by activating the immune system, and combined with existing anticancer drugs can enhance the anticancer effect. Compared with the traditional chitosan, hydroxypropyl chitosan is a natural polymer chitosan derivatives, because the introduction of hydroxypropyl on chitosan, liver targeted chitosan nano carrier particles made of chitosan, targeted nano drug system, can slow release, controlled release, targeted release, increase drug absorption and bioavailability, reduce drug side effects of [10].

5. Chitosan nanoparticles connect the drugs to liver cancer

5-Fluouracil (5-Fu) is one of the broad spectrum anti-tumor drugs commonly used in clinical practice. The targeted research of 5-Fu is particularly important. Current research of liver targeting system is divided into passive targeting method and active targeting method. Passive targeting of 5-Fu can be achieved by sealing 5-Fu with nanopadministration system and tumor Enhanced Permeability and Retention effect (EPR effect), while active targeting can be achieved by binding surface grafting ligands

ISSN 2618-1584 Vol. 4, Issue 8: 15-18, DOI: 10.25236/FMSR.2022.040804

in nanopadministration system and receptor highly expressed in tumor cells. The desialate glycoprotein receptor (ASGPR) on the surface of hepatocytes can specifically recognize the galactose residues of the dessialate glycoprotein and remove its endocytosis. Recently, it has been extensively studied as an effective target for active liver targeting.

6. Expanding application of chitosan nanoparticles

6.1. Improve drug utilization

Studies have been conducted to form nanoparticles through the interaction of negatively charged soybean ooithin with positively charged chitosan. Nanoparticles were also characterized by differential scanning calorimetry and by an FT-IR spectrophotometer. Drug-loaded nanoparticles do not induce a significant reduction in cell viability. Pharmacokinetic studies in female Wistar rats demonstrated a significant improvement in oral bioavailability (4. 2-fold) after drug loading into nanoparticles. Furthermore, modified valgus sac studies suggest that these nanoparticles are absorbed by active endocytotic processes in the gut. In vitro mucosal adhesion studies have demonstrated that nanoparticles bind to the mucus layer of the gut, which has in turn been associated with reduced excretion of drugs in the feces. In conclusion, the proposed nanoparticles appear to be effective in oral drugs with poor bioavailability, such as raloxifen hydrochloride [12].

Biopolymer-based nanoparticle delivery alternated to improve the bioavailability of nutritional health products and drugs. Intetphysiology suggests that the lipid fraction is required for lipid absorption. To assess the bioaccessibility of chlorophyll-encapsulated chitosan nanoparticles with PC (LCNPC) or without PC (LCN), cellular uptake / internalization, and basolateral secretion of lutein in Caco-2 cells. In LMM, lutein uptake was maximal at 8 h and gradually decreased for maintenance release response in LCNPC and LCN, while lutein uptake from GMM was quite low at all time points. These results suggest that the preparation of biopolymer-based nanoparticles with PC can provide greater insight to improve lutein bioavailability at the level of intestinal epithelial cells [13].

6.2. Used as an anticancer agent

Studies have used curcumin combined with (±) -lipoic acid as an active agent for preparing phosphorylated chitosan nanoparticles. The ion gel method was used for the successful preparation of nanoparticles. Fourier transform infrared spectroscopy (FT-IR) and X-ray diffraction instrument (XRD) reveal the effective binding of drugs in the polymer system. The morphology and size characteristics of the nanoparticles were analyzed by scanning electron microscopy, transmission electron microscopy and dynamic light scattering. The swelling degree and the drug release mechanism at different times at pH 5. 0 and 7. 4 were investigated by a UV-visible spectrophotometer. Cytotoxicity studies were performed on normal human lymphocytes and MDA MB 231 breast cancer cell lines by MTT analysis. The blue dye rejection assay was performed to confirm the anticancer effect of nanoparticles. The nature of the prepared nanoparticles recommended their possible use as the anticancer agent [14].

6.3. Targeted therapy

The development of a non-toxic, targetable and effective small interfering RNA (siRNA) delivery system remains a major challenge for the clinical application of siRNA therapy. Nanoparticles of carboxymethylchitosan (CMC) and labeled fluorescein isothiocyanate (FITC) -chitosan hydrochloride (CHC) are delivered as ultrasound-triggered drug delivery for colon cancer. The results show that the (FITC-CHC) -CMC nanoparticles can improve the stability of siRNA, and the (FITC-CHC) -CMC-based pH-sensitive delivery system can achieve a controlled release of siRNA by responding to external stimuli (ultrasound) under favorable pH conditions. An effective reduction in proteins that promote colon cancer proliferation. Our results suggest that the siRNA- (FITC-CHC) -CMC delivery system has great potential for for RNAi therapy in diseased cells [15].

7. Conclusion and Outlook

Chitosan has been well used in slow and controlled release preparations of drugs and targeted therapy for tumors. Due to its unique physicochemical properties and biological characteristics, chitosan is widely used in targeted drug delivery system as a slow and controlled release agent, mucosal adsorbent,

ISSN 2618-1584 Vol. 4, Issue 8: 15-18, DOI: 10.25236/FMSR.2022.040804

absorbent and penetration promoter, macromolecular agents, disintegrants, coating materials and other drugs (or proteins, peptides, genes) carriers. Through various local administration or site-specific administration, it can extend the exposure time, improve the drug absorption, enhance the efficacy, and reduce the adverse reactions. With the increasing exhibition of scientific and technological means and the increasing progress of physical and chemical methods, chitosan preparations will be more improved and developed.

Acknowledgements

This work was financially supported by Shaanxi College Students' innovation and entrepreneurship training program (No.: S202010716049).

References

[1] Li G Y, Zhong M, Zhou Z D, et al. Novel carboxymethyl chitosan microspheres for controlled delivery of chel- erythrine [J]. Journal of Macromolecular Science Part A-Pure Applied Chemistry, 2011, 48(11): 904-911.

[2] Monier M. Adsorption of Hg^{2+}, Cu^{2+} and Zn^{2+} ions from aqueous solution using formaldehyde cross-linked modi- fied chitosan-thioglyceraldehyde Schiff's base [J]. Int J Biol Macromol, 2012, 50(3): 773-781.

[3] ElSerag H B,Mason A C. Risk factors for the rising rates of primary liver cancer in the United States. [J]. Archives of internal medicine, 2000, 160(21).

[4] Niu Jianjun. Association studies of environmental factors, long non-coding RNA and primary hepatocellular carcinoma in men [D]. Xiamen University, 2019. DOI: 10. 27424/d. cnki. gxmdu. 2019. 000553.

[5] Zhu Guowang. Biological gene therapy for liver cancer is worth exploring [N]. China Medical News, 2010-06-29(B03). DOI:10. 38249/n. cnki. nyiya. 2010. 002383.

[6] Elisa Franco Ribeiro,Taís Téo de Barros-Alexandrino, Odilio Benedito Garrido Assis, Américo Cruz Junior, Amparo Quiles, Isabel Hernando, Vânia Regina Nicoletti. Chitosan and crosslinked chitosan nanoparticles: Synthesis, characterization and their role as Pickering emulsifiers [J]. Carbohydrate Polymers, 2020, 250.

[7] Zhang Wei. Demethypiegrin low molecular weight chitosan nanoparticle study [D]. Suzhou University, 2008.

[8] WJ Lin, MH Chen. Synthesis of multifunctional chitosan with galactose as a targeting ligand for glycoprotein receptor [J]. Carbohydr Polym, 2007, 67 (4): 474-480.

[9] Illum L , Farraj N F , Davis S S . Chitosan as a Novel Nasal Delivery System for Peptide Drugs[J]. Pharmaceutical Research (New York), 1994, 11(8):1186-1189.

[10] Bodnar M, Hartmann J F, Borbely J. Preparation and characterization of chitosan -based nanoparticles [J]. Biomacromolecules, 2005, 6 (5): 2521-2527.

[11] Song Peng. Preparation of novel amphipathic chitosan derivatives and their application in drug carriers [D]. University of Ji'nan, 2012.

[12] Liu Fang. Preparation of folate-targeted TFPI-2 and cisplatin magnetic nanocomplexes and targeted treatment of nasopharyngeal carcinoma [D]. Southern Medical University, 2015.

[13] Ma Baohua. Preliminary study of chitosan-modified TFu solid lipid nanoparticles [D]. Shandong University, 2009.

[14] Hulikere Jagdish Shwetha, Shivaprasad Shilpa, Mousumi Beto Mukherjee, Rudrappa Ambedkar, Ashok M. Raichur, Rangaswamy Lakshminarayana. Fabrication of chitosan nanoparticles with phosphatidylcholine for improved sustain release, basolateral secretion, and transport of lutein in Caco-2 cells [J]. International Journal of Biological Macromolecules,2020,163.

[15] Plabita Gogoi, Anindita Dutta, Anand Ramteke, Tarun Kumar Maji. Preparation, characterization and cytotoxic applications of curcumin-(±) α-lipoic acid coloaded phosphorylated chitosan nanoparticles in MDA MB 231 breast cancer cell line [J]. Polymers for Advanced Technologies, 2020, 31 (11).

[16] Ling Yan, Shengjie Gao, Shanshan Shui, Shuai Liu, Hao Qu, Changhong Liu, Lei Zheng. Small interfering RNA-loaded chitosan hydrochloride/carboxymethyl chitosan nanoparticles for ultrasound-triggered release to hamper colorectal cancer growth in vitro [J]. International Journal of Biological Macromolecules, 2020, 162.