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Drug Design 2020: Drug delivery system targeting advances hepatocellular carcinoma- Hong Qi Zhang- Hong Kong Baptist University

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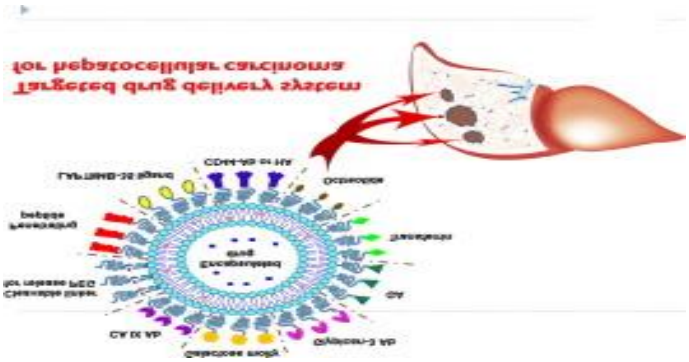
Hepatocellular carcinoma (HCC) is one of the predominant forms of liver cancer and accounts approximately for 90% of total hepatic malignancy. Systemic chemotherapy is preferred in patients with advanced HCC. Conventional chemotherapy is less effective in treating HCC essentially due to the poor specificity of these agents to malignant tumor cells. In addition, the non-selectivity of chemotherapeutic drugs frequently causes severe toxic side effects that often limit dose escalation, undesirable bio distribution, poor response, rapid clearance, quick disease relapse, and eventually drug resistance. Thus, developing new treatment paradigms to provide optimal treatment for HCC has become a fascinating topic in drug delivery research. Current therapeutic strategies in HCC aim to improve the clinical potential of chemotherapeutic agents by targeting them to the tumor site. Various targeting approaches have been explored to improve the pharmacotherapy of cytotoxic agents by delivering them to the tumor cells. Among these, the active targeting of anticancer drugs by developing carrier systems with specific ligands has attained much attention. Typically, these nano sized ligand-bound systems will potentially transport the drug to the tumor site and bind effectively to the overexpressed target receptors in cancer cells. The prospective of lipid and polymer-based carriers coupled with ligands has been extensively explored during the last few decades and has found some encouraging results. Lipid-based formulations such as liposomes, micelles, and emulsions with diverse ligand moieties to target liver cells have been developed. Alternatively, nucleic acids, proteins, and peptides have been explored to targeted liver cancer. On the other hand, polymeric nano carriers have also demonstrated certain progress in targeting cancer cells in absence of ligands due to their higher permeability to the tumor vasculature, along with an enhanced permeability and retention effect. Nevertheless, the pharmacological and therapeutic responses are improved when these carriers are combined with ligands.

Hepatocellular carcinoma (HCC) is notoriously difficult to treat thanks to its usually late detection and drug resistance to chemotherapy, making it one among the cancers with top deathrate . High dose of chemotherapeutic agents are often associated with intolerable side-effects. Targeted drug delivery systems (DDS) which will deliver therapeutic drugs selectively into cancer cells have shown an excellent potential in modern oncology, and various preclinical studies of DDS have been published in recent years. Yet targeted DDS for HCC has got to be made for practical clinical use to beat the obstacles of conventional chemotherapy. A good targeted drug delivery system design should take cancer-specific properties into consideration for effective drug delivery. The following biological and physicochemical properties of HCC are of use within the design of effective targeted DDS: (a) the blood supply of advanced HCC is especially from the arterial systems, (b) the micro vessel density is inversely correlated to HCC tumor size, (c) the tumor microenvironment of HCC is hypoxia and acidotic, with increased interstitial fluid pressure, and (d) there's an overexpression of proteins or receptors on HCC surface rather than normal hepatocytes like Glycan-3, asialoglycoprotein receptor, the transferrin receptor, carbonic anhydrase IX, and therefore the somatostatin receptor. A good targeted DDSs should make an honest use of those features of HCC for site-specific or targeted-oriented delivery in targeting either HCC vasculature and/or cellular components. Our recent experiments designed based on these considerations have indeed shown some promising results. These drug delivery systems will provide a efficient platform for future development of HCC treatments.



Hepatocellular carcinoma (HCC) plays a highly morbid role and treatment of hepatocellular carcinoma is very difficult because of long latent period before detection, multi-drug resistance and major drug-related adverse effects from chemotherapy. Targeted drug delivery systems (DDS) which can deliver therapeutic drugs through selective manner into tumor sites have developed a superb potential in cancer treatment, which could be utilized to resolve or decrease the limitations of conventional chemotherapy. Numerous preclinical studies of DDS are published, but targeted DDS for HCC has yet to be made for practical clinical use. Since rational targeted drug design systems design must take cancer-specific or related properties into consideration, we've reviewed the physiochemical and biological properties of hepatocellular carcinoma extensively to provide a comprehensive understanding on hepatocellular carcinoma, and recent DDS studies on hepatocellular carcinoma, going to find some potential targeted drug delivery systems for hepatocellular carcinoma treatment and a meaningful platform for further development of hepatocellular carcinoma treatments. Hepatocellular carcinoma features a high incidence worldwide and is understood to be multidrug resistant. Thus, intensive research is being administered to seek out better chemotherapeutic agents also as new drug delivery systems. In this ab-

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stract, the authors reviewed thoroughly the present challenges facing new drug designs and also outlined novel targeted drug delivery systems (DDS) within the fight against hepatocellular carcinoma.

Keywords:
Targeted drug delivery systems, Liver cancer, Advanced hepatocellular carcinoma, Nanomedicine.

Abbreviations:
HCC-hepatocellular carcinoma; DDS-drug delivery system; ECM-extracellular matrix; MVD-microvessel density; EPR-enhanced permeability and retention; ASGP-R - asialoglycoprotein receptor, GPC3-glypican 3; HS chain-heparin sulfate chain; GA-glycyrrhetinic acid; TfR-transferrin receptor; Extraextracellular domain; Trans, transmembrane domain; Intra, intracellular domain; SSTR, somatostatin receptor.

Conclusion:

The pathogenesis of liver diseases involves a variety of cells which makes the delivery of drug complicated. The most important aspects to improve the treatment via hepato protective drug are the design and synthesis of appropriate polymeric material to target specific cells of liver. Ingenious studies are required in coupling and selection of targeting moiety so that they could be translated from the bench research to the bedside. We have reviewed various aspects of selection of ligands and their coupling to drug/polymer which would potentially target parenchymal/non-parenchymal liver cells. The physiochemical factors and pharmacokinetic behavior related with drug delivery systems have been considered to be majorly responsible for the improved therapeutic and targeting effectiveness; therefore, dealing with these factors during development of formulation could lead to more promising treatments for acute and/or chronic liver diseases. These investigations require thorough inspection as well as innovative approaches to bring them into the global market at affordable price

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