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Navigating the Future: Nanotechnological Strategies for Tackling Hepatocellular Carcinoma

Annu Kumari[1]*, Swati Chowdhury[1], Disha Agarwal[1], P Wankitlang Shangpliang[2], Ritu Sharma[3] and Aquisha Suklin Lanong[4]

[1]The Assam Royal Global University, Department of Zoology, Guwahati, Assam 781035, India

[2]Zoology Department, St. Edmund's College, Shillong 793003, Meghalaya, India

[3]Darrang College, Zoology Department, Tezpur-784001, Assam, India

[4]North Eastern Hill University Shillong-793001, Meghalaya, India

ABSTRACT

Hepatocellular carcinoma (HCC), a widely prevalent form of liver malignancy, is a leading contributor to cancer-related mortality globally, despite advances in preventive and diagnostic technologies. It is closely associated with cirrhosis, with major contributions from hepatitis B and C infections and alcohol consumption. Early detection of HCC is crucial as it is often diagnosed at an asymptomatic stage. Radiological screenings and serological markers are effective methods of achieving early detection. Various surgical methods, including liver transplantation, and therapies such as radiofrequency lesioning and chemoembolization, are employed to treat this disease. However, due to limited donor availability and late diagnosis, treatment can be delayed. Tumour size, liver disease severity, and patient's overall health are among the factors that influence the disease. Nanotechnology, a field that involves the precise manipulation of materials at the nanometer scale and the targeted delivery of therapeutic agents, presents a promising solution for HCC therapy. The utilization of nanoparticle-based therapies allows for the specific targeting of tumour-associated antigens, which enhances drug delivery and reduces drug-induced toxicity. Furthermore, nanomaterials such as carbon nanoparticles and biochemical sensors aid in the detection of oncological markers. Nanomedicine-based approaches possess the potential to revolutionize HCC therapy by improving drug delivery and targeting liver cancer stem cells. Specifically, targeted ligand-mediated therapy using saccharide or polysaccharide compounds, antibodies, peptides, and aptamers shows promise for liver-specific HCC treatment. Additionally, nanotherapy aimed at liver cancer stem cells (LCSCs) provides new possibilities to overcome the limitations of conventional treatments and improve patient outcomes. Ultimately, nanotechnology-based approaches hold great potential in enhancing the effectiveness of HCC therapy and offer new avenues for precision medicine in cancer treatment.

***Corresponding author's**

Annu Kumari, The Assam Royal Global University, Department of Zoology, Guwahati, Assam 781035, India.

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Introduction

Cancer is one among the preeminent contributor to mortality on a global scale [1]. Hepatocellular carcinoma, commonly referred to as HCC, has emerged as the most frequently encountered variant of malignancy in the liver. The mortality rate of this disease is quite high worldwide. Regardless of all the new preventive technologies for both diagnosis and prognosis, until now, it remains as the foremost factor contributing to fatalities caused by cancer. Hepatitis B & C play individualistic roles to develop cirrhosis. Alcohol consumption is positively associated with an elevated risk of developing cirrhosis. The detection of this disease can be confirmed by using radiological screenings such as computerized tomography (CT scan), ultrasound, magnetic resonance imaging (MRI), and the use of serological markers such as α-fetoprotein, have been employed at intervals of six month [2]. Usually, the disease is confirmed at an asymptomatic stage in most of the patients. The notable factors to be taken into account are the tumour size, acuteness of any primary liver disease and also the overall health condition of the patient. Surgical methods such as liver transplantation is an effective way of treating this lethal disease but certain factors like limited availability of donors and late diagnosis might delay the treatment [3].

The treatment methods for this disease includes incision of the liver, radiofrequency lesioning, transcatheter arterial chemoembolization. Incision of liver is not recommended to every patient of HCC [4]. It is only performed in patients at the very beginning of malignancy. Some of the post-hepatectomy symptoms in patients include leakage of bile fluids, hepatic failure, fever and also low level of tolerance in patient's post-surgery [5]. The chances of hepatic cancer can be increased by hepatic fibrosis, chronic hepatitis, non-alcoholic fatty liver disease (NAFLD), aflatoxicosis etc. The manifestation of HCC is heavily influenced by genetics, implying a crucial role of genetic factors in its emergence [6]. Nanotechnology, a pioneering scientific methodology utilized for the precise design of materials at the nanometer scale, incorporating biomimetic, biological, and biologically-inspired molecules. Applications of chemistry, biology and quantum mechanics is used in this field. Based on three features i.e., direct, indirect and conceptual, nanotechnology is often regarded to be an innovative tool [7]. Throughout the years, by the use of nanotechnology the various immunotherapeutic agents have been used for several cancer types hence reducing the malignancy [8].

The conventional methods for detecting and treating HCC is less effective when compared to modern practices of nanotechnology since the particles have high responsiveness, reduces drug-induced toxicity and it can also be fused with 'theranostics' [9]. One of the foremost challenges in the domain of oncological treatment concerns the phenomenon of drug non-responsiveness, which can be triumphed over through the application of nanoparticle-based therapies that are specifically directed towards tumour-associated antigens (TAAs) in order to enhance drug delivery [10]. Nanotechnological activities helps to understand life processes at a more molecular-scale domain [6]. Different types of nanomaterials assist in locating oncological markers exclusively and receptively. The nanomaterials include nano-carbon particles, nanocrystal, carbon nanotubes (CNTs), biochemical sensors, etc [11].

What is Hepatocellular Carcinoma?

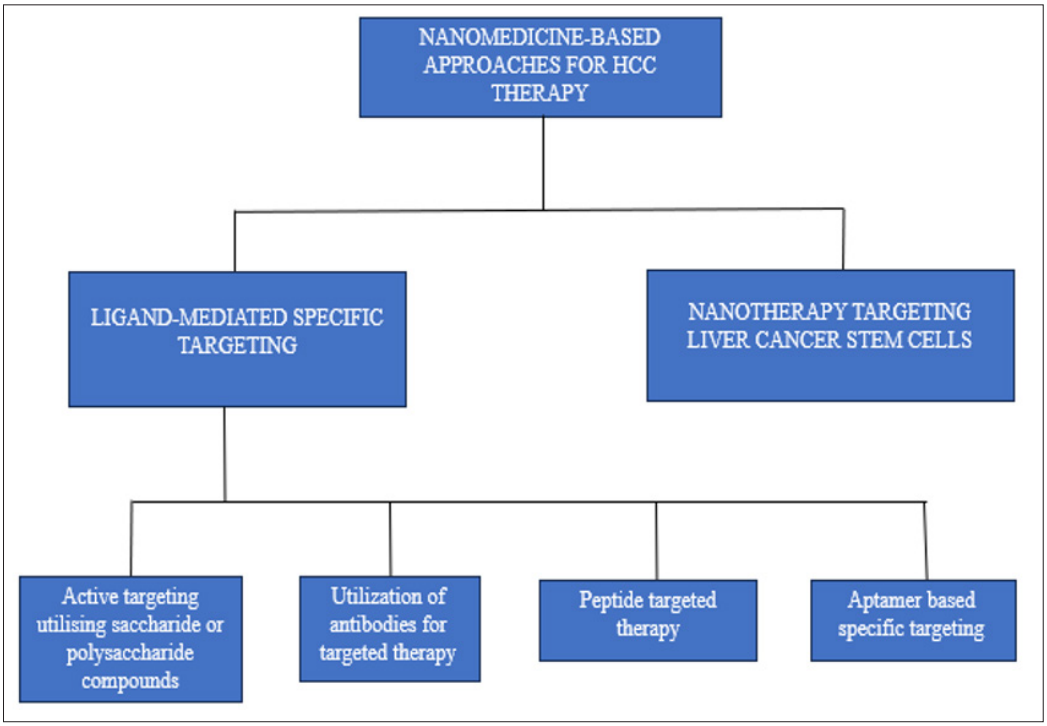

Figure 1: A Schematic Flowchart Showing Various Nanotechnology Applications used for the Treatment of HCC

Hepatocellular carcinoma, the primary form of malignancy, is widely considered one of the foremost contributors to cancer-related mortality on a global scale. The initial cause of this disease is the beginning of cirrhosis. One of the major factors for this disease is the consumption of alcohol [12]. People suffering from diabetes mellitus have a high chance of getting exposed to HCC. Even if HCV is treated, there is still high chances of a person likely to contract HCC if the patient has cirrhosis [13].

Diagnosis is ascertained in the absence of pathological substantiation. Multiple therapeutic approaches are at our disposal; nonetheless, solely orthotopic hepatic transplantation (OHT) or surgical excision can provide a cure. Hepatocellular carcinoma (HCC) may be averted through the implementation of appropriate measures, such as the administration of vaccination against hepatitis B virus, the adoption of universal testing of blood donors, the usage of safe injection techniques, the provision of medical care and guidance to those suffering from alcohol addiction and intravenous drug abusers, and also the antiviral treatment initiation. The sustained enhancement in operative and non-operative techniques has evinced noteworthy advantages within the realm of overall longevity [14]. Observational investigations have exhibited that the probability of acquiring HCC is primarily influenced by key factors, namely infection age, masculine gender, and ongoing liver injury associated with viral reactivation [15].

Nanomedicine-Based Approaches Hepatocellular Carcinoma (Hcc) Therapy

Conventional therapeutic modalities for hepatocellular carcinoma (HCC) treatment, such as cancer therapy, radio-oncology, and surgical treatment, are the prevailing approaches worldwide to manage malignancy, albeit with certain limitations. These drawbacks comprise of the unspecified dispersion throughout the organism and non-selective administration of therapeutic agents, leading to inadequate dosing of anticancer medications within the targeted tumour microenvironment, along with certain constraints in bio-imaging and diagnosis (Wang et al., 2008) [16]. On the contrary, the efficacy of hepatocellular carcinoma (HCC) therapy is considerably deficient owing to the elevated incidence of recurrence and the unyielding nature of anticancer medications [17].

Ligand-Mediated Specific Targeting

Active Targeting Utilizing Saccharide or Polysaccharide Compounds

Glycoproteins and proteoglycans, attached to protein molecules, exhibit a diverse range of glycans on the external layer of malignant cells. These glycans are commonly observed to undergo upregulation when compared to their healthy cell counterparts. This upregulation makes saccharides or polysaccharides promising candidates to act as ligand molecule for liver-specific targeting [18].

The discovery and characterization of the asialoglycoprotein receptor (ASGPR), also known as the Ashwell-Morell receptor which was first identified and investigated by Baenziger and Maynard, is particularly notable [18].

Utilization of Antibodies for Targeted Therapy

The present study concerns the advancement of therapies that target cancer by merging the specific binding of antibodies is highly correlated with the effectiveness of potent small molecule chemotherapeutics, commonly known as antibody-drug conjugates (ADCs). ADCs consist of an antibody that has a covalent linkage to an anticancer drug. This antibody specifically binds to an antigen that is prominently found on malignant cells. The cell internalizes the conjugate, which subsequently discharges a potent anticancer drug that effectively eradicates the neoplastic cell. There exist numerous obstacles in the process of advancing ADCs, which includes complications related to the stability and half-life of the ADC within the plasma as well as its efficient transportation from the blood into the tumour compartment, the expression of cancer cell antigens, and the binding affinity of the ADC with the specific antigen, the internalization mechanism of the ADC by the cancer cells, the separation of the anticancer medication from the ADC, and the cytotoxic impact of the medication on the designated cells [19].

Peptide-Targeted Therapy

In the subsequent section, certain extensively examined CCAs, namely glypican-3 (GPC3), alpha-fetoprotein (AFP), WT-I, Forkhead box protein M1 (FOXM1), and Roundabout guidance receptor 1 (ROBO1), have been identified as being overexpressed in HCC and may be utilized for peptide vaccines comprising of anticipated or purified peptides. The cancer-associated antigens (CAAs) present in hepatocellular carcinoma are characterized by overexpression, signifying that the tumour cells generate a substantial amount of messenger ribonucleic acid (mRNA) and amino acid chains of these CAA in comparison to healthy tissues. Therefore, it is widely recognized that roughly one peptide per ten thousand degraded proteins is exhibited to MHC [20]. Additionally, given that production of major histocompatibility complex class I (MHC-I) peptides is associated with the amount of mRNA, it is plausible to consider that excessively expressed cancer-associated antigens are promising onco-antigen candidates for cancer vaccines [21].

Aptamer Based Specific Targeting

Among the various ligands investigated by scholars with the intention of developing focused therapy for hepatocellular carcinoma, the utilisation of aptamers for neoplastic hepatocyte targeting has garnered considerable traction in comparison to other cell-targeting ligands for HCC, including antibodies, peptides, 2-amino-2-deoxygalactose and transferrin. This phenomenon can be attributed to several widely recognized aptamer characteristics, including their modest molecular weight, heightened selectivity and avidity towards the molecules that are intended targets, absence of immunogenicity, superior tissue permeation capacity, heat stability, as well as their facile modifiability and production capabilities [22-24]. Aptamers, synthesized chemically as short oligonucleotides of DNA/RNA, possess unique three-dimensional structures that account for their remarkable specificity and affinity towards target molecules. This exclusive attribute renders them with an exceedingly promising potential as a ligand in the domain of precision medicine [23,24].

Nanotherapy Aimed at Liver Cancer Stem Cells (LCSCs)

Three decades ago, the capacity of stem cells' capacity to undergo malignant transformation was made, subsequently leading to the identification of cancer stem cells (CSCs) within distinct tumours. CSCs are characterized by similarities to regular stem cells, as they possess the capacity of self-renewal and exhibit pluripotency, in addition to a propensity for heightened degrees of carcinogenicity and drug resistance [25,26]. Henceforth, it is imperative to devise innovative therapeutic techniques to surmount the constraints of conventional treatments which have proven to be ineffective against cancers originating from stem cells. In liver cancer, for instance, the demonstration of the presence of Cancer Stem Cells (CSCs) has been conducted by identifying particular cell surface biomarkers such as CD133, CD44, CD90, among others [27].

Discussion

Hepatocellular Carcinoma (HCC), recognized as the most prevalent form of intrahepatic carcinoma, is acknowledged as a significant contributor to carcinoma-related mortality worldwide. The ailment is closely associated with liver cirrhosis, and risk factors such as infections caused by hepatitis B and C and alcohol consumption are known to contribute to its development [28]. During the subclinical phase, HCC is frequently evaluated using a range of radiological screens and serological markers. The treatments available for HCC include transcatheter arterial chemoembolization, radiofrequency lesioning, liver incision, and liver transplantation. Furthermore, HCC's manifestation is influenced by genetic parameters [29].

The present study focuses on Nanomedicine-based approaches for the treatment of Hepatocellular carcinoma (HCC). The study sheds light on the limitations of conventional therapy approaches used for HCC treatment, such as non-targeted drug application and insufficient dosage within the tumour microenvironment [30]. Nanotechnology offers promising solutions to these challenges. Specifically, nanoparticle-drug formulations enable site-specific drug delivery, thereby mitigating drug toxicity. Nanoparticles also facilitate bio visualization and clinical investigation. Research has been conducted on a range of nanomaterials, including carbon nanotubes, nano-carbon particles, and biochemical sensors, for the purpose of diagnosing and treating HCC [31].

The book explores the use of ligand-mediated selective targeting, which involves saccharide or polysaccharide molecules capable of targeting the liver [32]. The asialoglycoprotein receptor (ASGPR) is identified as a pivotal target for this purpose. Furthermore, peptides and antibodies are being studied as ligands for targeted therapy.

Aptamers, which are chemically engineered short DNA/RNA oligonucleotides, have been the subject of much attention due to their specificity, selectivity, lack of immunogenicity, and other advantageous characteristics. Particularly for neoplastic hepatocyte targeting, aptamers have shown great promise. As ligands, they have potential for precision medicine.

The text highlights the existence of cancer stem cells (CSCs) present within liver tumours. These CSCs manifest self-renewal and pluripotency traits and are associated with resistance to medication. Liver cancer stem cells (LCSCs) are the intended recipient of nanotherapy [33].

This innovative approach to treatment aims to overcome the constraints of traditional therapies by specifically targeting LCSCs. As such, extensive research is underway in the area of nanotherapy that is geared towards LCSCs. The present paper presents a

comprehensive overview of Hepatocellular Carcinoma (HCC), encompassing its diagnosis and conventional treatment options. A particular emphasis is placed on exploring the potential of ligand-mediated specific targeting and aptamer-based techniques, and their role in facilitating nanotechnology and nanomedicine-based approaches for effective and targeted therapy.

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