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Recent advances in hepatocellular carcinoma therapy☆

Rinku Dutta, Ram I. Mahato *

Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, NE 68198, United States

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ABSTRACT

Hepatocellular carcinoma (HCC), also called malignant hepatoma, is one of the deadliest cancers due to its complexities, reoccurrence after surgical resection, metastasis and heterogeneity. Incidence and mortality of HCC are increasing in Western countries and are expected to rise as a consequence of the obesity epidemic. Multiple factors trigger the initiation and progression of HCC including chronic alcohol consumption, viral hepatitis B and C infection, metabolic disorders and age. Although Sorafenib is the only FDA approved drug for the treatment of HCC, numerous treatment modalities such as transcatheter arterial chemoembolization/transarterial chemoembolization (TACE), radiotherapy, locoregional therapy and chemotherapy have been tested in the clinics. Polymeric nanoparticles, liposomes, and micelles carrying small molecules, proteins, peptides and nucleic acids have attracted great attention for the treatment of various cancers including HCC. Herein, we discuss the pathogenesis of HCC in relation to its various recent treatment methodologies using nanodelivery of monoclonal antibodies (mAbs), small molecules, miRNAs and peptides. Synopsis of recent clinical trials of mAbs and peptide drugs has been presented with a broad overview of the pathogenesis of the disease and treatment efficacy.

Contents

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and rank third in cancer-related deaths globally considering malignancies, severity, treatment challenges and 5-year survival rate (< 5 %) among cancer patients (Cabibbo, Latteri, Antonucci, & Craxi, 2009; Singh, Singh, Roberts, & Sanchez, 2014). Among various types of primary hepatic neoplasms such as cholangiocarcinoma (bile duct cancer of biliary epithelial cells), hepatoblastoma (rare early childhood malignant liver tumor), bile duct cystadenocarcinoma and epitheliod

Abbreviations: AASLD, American Association for the Study of the Liver Disease; AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartase aminotransferase; AFP-L3, agglutinin reactive fraction of AFP; cccDNA, covalently closed circular DNA; CTL, cytotoxic T lymphocyte; DAA, direct-acting antivirals; DOX, Doxorubicin; ERK, Extracellular signal-regulated kinase; GPC3, Glypican-3; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HCC, Hepatocellular carcinoma; HLA, human leukocyte antigen; JNK, Jun amino-terminal kinases; LCN, liquid crystalline nanoparticles; LP, liposomes; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; mAbs, monoclonal antibodies; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver diseases; PDGF, platelet derived growth factor; PEG, polyethylene glycol; ROS, reactive oxygen species; TACE, Transarterial chemoembolization; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial growth factor.

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* Corresponding author at: Department of Pharmaceutical Sciences, University of Nebraska Medical Center, 986025 Nebraska Medical Center, Omaha, NE 68198, United States.
E-mail address: ram.mahato@unmc.edu (R.I. Mahato).

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haemangioendothelima, HCC deserves special mention (Farazi & DePinho, 2006). The stimulus for HCC development in Asian and African countries arises from factors like chronic hepatitis B and C viral infection, chronic alcohol consumption, aflatoxin-contaminated food intake, other hereditary diseases (hemochromatosis due to iron overload in the body) and liver cirrhosis (Farazi & DePinho, 2006; Ge & Huang, 2015; Ghasemi, Rostami, & Meshkat, 2015). In the developed countries, the epidemiological evidence connecting the pathologies are type 2 diabetes, obesity, metabolic disorders and non-alcoholic steatohepatitis (NASH) as part of non-alcoholic fatty liver diseases (NAFLD) (Reeves, Zaki, & Day, 2016; Trojan, Zangos, & Schnitzbauer, 2016). The risk factors susceptible for the occurrence of HCC are more common in the male population compared to the females (4:1) (Yang, Ekanem, Sakyi, & Ray, 2015). Other factors such as age, tyrosinemia, galactosidemia, fructosemia, and hypothyroidism also play critical roles in the prevalence of HCC (Mazzanti, Arena, & Tassi, 2016; Zhu, Seto, Lai, & Yuen, 2016). Although surgical resection is the only curative therapy, it often causes hindrance to most patients detected at late stage of the disease. Following resection, the survival rate reaches 70 % if the tumor is < 2 cm (Varshosaz & Farzan, 2015). As a result, early diagnosis is crucial for successful treatment. Computed tomography (CT), magnetic resonance imaging (MRI), ultrasound and dynamic multiphasic multi-detector-row CT (MDCT) are the standard HCC diagnostic methods (Bertino et al., 2014; Daoudaki & Fouzas, 2014). Based on the tumor size, serum albumin, bilirubin and α-fetoprotein (AFP) levels, HCC morphology, presence of portal vein thrombosis and ascites, various classifications are used in order to categorize the stage of the disease, particularly Okuda staging system (I-III), Cancer of Liver Italian Program (CLIP) score (0-6), Barcelona Clinic Liver Cancer (BCLC) (Table 1), American Association for the Study of the Liver Disease (AASLD), National Comprehensive Cancer Network (NCCN) and European Association for the Study of the Liver (EASL) are noteworthy (Bertino et al., 2014; Trojan et al., 2016). Apart from liver transplantation, tumor local ablation, embolization, (Transcatheter arterial chemoembolization/transarterial chemoembolization or TACE) and chemotherapy are often recommended for patients with BCLC stage B-C (Table 1) (Bruix et al., 2011; Trojan et al., 2016). Advanced stage HCC leads to aggravated liver dysfunction, making systemic drug delivery ineffective. Also, development of drug resistance and untoward systemic side effects cause serious obstacles to successful treatment regimen for HCC. In practice, the usual biomarkers for the detection of HCC are serum alanine aminotransferase (ALT), aspartase aminotransferase (AST) and alpha-fetoprotein (AFP). In addition, other biomarkers such as glypican-3 (GPC-3), des-carboxyprothrombin (DCP), *lens culinaris*-agglutinin reactive fraction of AFP (AFP-L3), human hepatocyte growth factor (HGF), insulin-like growth factor (IGF), chromogranin A (CgA), osteopontin (OPN), alpha-1-fucosidase (AFU) and squamous cell carcinoma antigen-immunoglobulin M complexes (SSCA-IgM Cs) alone or in combinations are helpful in early detection of HCC (Bertino et al., 2014; Kondo, Kimura, & Shimosegawa, 2015; Yang et al., 2015). (See Figs. 1–3.)

Table 1
Classification of BCLC staging of hepatocellularcarcinoma.

	Barcelona-clinic liver cancer
Stage 0	Single nodule; <2 cm
Early stage (A)	HCC patients are asymptomatic; suitable or radical therapies; single or 3 nodules; <3 cm
Intermediate stage (B)	Asymptomatic and multinodular tumors, not suitable for resection but for palliative systemic therapy (sorafenib)
Advanced stage (C)	Symptomatic tumors, vascular invasion, extrahepatic spread, preserved liver function (child-pugh turcotte classification B), not suitable for resection but for palliative systemic therapy (sorafenib)
Stage (D)	Poor prognosis, Okuda stage III tumors, decompensated cirrhosis (child-pugh C)

HCC is mainly the cancer of liver parenchymal cells. Although most of the risk factors of the occurrence of this solid cancers are known, the underlying mechanisms responsible for the conversion of healthy hepatic cells to neoplastic ones are still ambiguous. Various strategies have been implemented for improving the clinical benefits and better therapeutic outcome. Alcohol intake prevention, vaccination against hepatitis B virus (HBV) infection, intake of vitamin D and calcium can prevent HCC in many cases but could not obliterate the disease. The occurrence of this multi-stage carcinogenesis evolves through dysregulation of multiple signaling pathways, genetic alterations with the initiation of inflammatory responses leading to the formation of a heterogeneous solid tumorous mass.

Specific drug delivery techniques have been proven to be efficacious with respect to better targeting and minimizing the adverse toxic effects to the surrounding organs. Targeting the receptors with peptide mediated drug delivery has significantly outweighed the adversities of chemotherapy. In this review, we discuss the causes and recent treatment modalities of HCC, with an emphasis on delivery and targeting of small molecules and RNAs with different synthetic carriers.

2. Causes for Hepatocellular Carcinoma

Multiple factors are responsible for the initiation and progression of HCC include (a) virus-induced, (b) alcohol-induced, (c) fungi-induced hepatocarcinogenesis, (d) obesity and type II diabetes (Fig. 1).

2.1. Virus-induced hepatocarcinogenesis

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infect approximately 2 billion and 170 million people worldwide, respectively (Farazi & DePinho, 2006; Tamori, Enomoto, & Kawada, 2016). Almost 2.5 % of the chronic HCV cases leads to HCC and the underlying virus-associated mechanisms is complex comprising both the host and viral factors where host-virus interactions lead to robust T-cell immune response elicitation (Colpitts & Baumert, 2016; Farazi & DePinho, 2006).

2.1.1. HBV

HBV belongs to the Hepadnaviridae family and apart from human hepatocytes it also infects birds and other animals (Farazi & DePinho, 2006; Levrero & Zucman-Rossi, 2016). The infectious HBV particle consists of a circular relaxed partially double-stranded DNA (covalently linked to a DNA polymerase) composed of 3200 nucleotides within the inner nucleocapsid which is in turn enveloped by a spherical lipid layer. The nucleocapsid is composed of core protein HBcAg and the membrane with 3 surface proteins HBsAg (according to sizes; preS1 (large), preS2 (middle) and preS3 (small)) along with host-derived lipids (Levrero & Zucman-Rossi, 2016). For infection the virion first attach to the cellular heparan sulfate proteoglycan (HSPGs) and subsequently bind to the hepatocyte-specific receptor irreversibly. Recently, the role of transmembrane transporter Na^+-taurocholate *co*-transporting polypeptide (NTCP) has been elucidated to which the virus bind utilizing the preS1 domain (Zhang, Zehnder, Damrau, & Urban, 2016). Following entry within the hepatocytes via endocytosis, infection takes place in three steps, (i) viral polymerase expulsion, (ii) positive DNA strand completion and (iii) the HBV DNA conversion to covalently closed circular DNA (HBV cccDNA) and incorporation of histone and non-histone proteins to form minichromosome in the hepatocyte nucleus. Viral replication through infection of hepatocytes is manifested by cccDNA minichromosome which serves as the viral mRNA transcription template by recruiting viral proteins (HBx and HBc), transcription factors, coactivators/corepressors and other enzymes necessary for chromatin modifications. Insertional mutagenesis, genomic stability and activation of pathways related to carcinogenesis by the viral proteins such as HBx, HBc and preS (both wild-type and mutated/truncated) are the different mechanisms promoting HCC by HBV. Various targeted cancer-related genes are involved in the integration of