Molecular Mechanisms and Targets of Therapy for Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. HCC develops through a multistep process that involves the local tumor microenvironment, intracellular signaling pathways, and altered metabolic system that allows the cancer proliferation. Understanding the mechanisms of tumor development and progression is critical to developing improved therapies aimed at better survival. This article reviews the molecular mechanisms of HCC development and highlights the potential therapeutic targets for treatments.

ABBREVIATIONS

AFB1 = aflatoxin B1, CSC = cancer stem cell, ECM = extracellular matrix, EMT = epithelial-mesenchymal transition, ERK = extracellular signal-regulated kinase, GH = growth hormone, HCC = hepatocellular carcinoma, HIF-1 = hypoxia-inducible factor-1, HK = hexokinase, HSP = heat shock protein, IGF = insulin-like growth factor, IL = interleukin, JAK = Janus kinase, MAPK = mitogen-activated protein kinase, SST = somatostatin

The prognosis of hepatocellular carcinoma (HCC) depends on the tumor stage at presentation and underlying liver function. The median survival of patients with untreated HCC is 9 months (1). The 1-year and 2-year survival rates for patients with untreated HCC are 17.5% and 7.3%, respectively (2). Primary treatment options for HCC are resection; transplant; and image-guided treatments, such as arterial embolization, transarterial chemoembolization, radioembolization, and ablation. Only 10%–23% of patients with HCC are appropriate surgical candidates for curative treatment (3). In a randomized controlled trial of transarterial chemoembolization versus conservative treatment, transarterial chemoembolization was associated with a significant improvement in median survival, demonstrating 1-year, 2-year, and 3-year survival rates of 82%, 63%, and 29% (4). However, transarterial chemoembolization is limited in its efficacy because it relies on delivering cytotoxic drugs, such as doxorubicin, into the hepatic artery. The choice of effective cytotoxic drugs is limited. Furthermore, embolization particles used to limit the perfusion to the region for chemoembolization cause devascularization leading to tissue hypoxia and necrosis, which have been demonstrated to increase inflammatory mediators and vasculogenic growth factors (5). New strategies are required for HCC treatment, and targeted drug delivery is emerging to be a preferred mode of therapy owing to the precision of the technique to deliver drugs to the specific location, avoiding peripheral distribution and side effects of drugs. The cutting-edge technology to design nanoparticles targeting specific cell surface receptors or molecular markers present in cancer cells promises improved HCC therapy and patient survival (6). The purpose of this article is to review the molecular mechanisms of HCC development and to highlight the potential therapeutic targets for improved HCC therapies.

FACTORS CONTRIBUTING TO HCC

The development of HCC is associated with 4 major factors: viral infections, hereditary disorders that alter intracellular pathways, chemical toxins, and metabolic syndromes (7). These factors regulate oxidative stress, cancer stem cells (CSCs), hypoxia, the hormonal system, the inflammatory/immune system, and the epithelial-mesenchymal transition (EMT), leading to the development of HCC (**Fig 1**).

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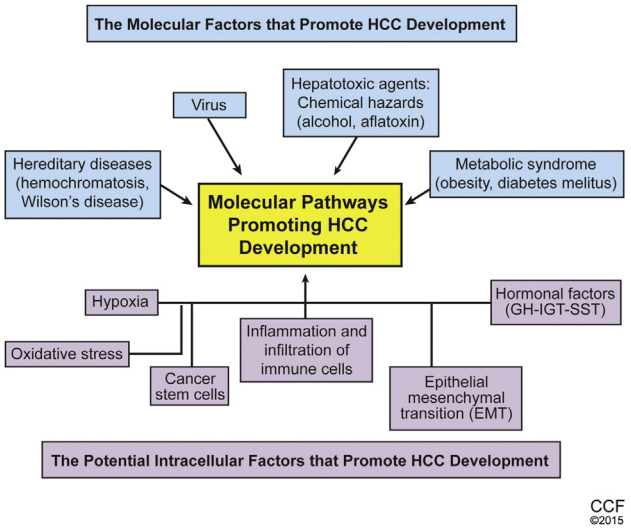

Figure 1. Factors involved in the development and progression of HCC. (Reprinted with permission of the Cleveland Clinic Center for Medical Art & Photography © 2016. All rights reserved.)

Viral Infections

Hepatitis B virus and hepatitis C virus can cause HCC in both direct (genomic mutation) and indirect (chronic inflammation) ways (8). The insulin-like growth factor (IGF) pathway plays a major role in cases of HCC caused by hepatitis B virus, especially in noncirrhotic liver (8). Viral proteins such as HBX and hepatitis C virus core regulate cell proliferation and work through the mitogen-activated protein kinase (MAPK) cascade and activate Ras-GTP to trigger the sequential activation of rapidly accelerated fibrosarcoma 1 (RAF-1), mitogen activated protein/ERK kinase 1/2, and extracellular signal-regulated kinase [ERK] 1 and 2, resulting in tumor progression (9,10).

Hereditary Diseases

HCC can also occur in patients with certain hereditary disorders, including hemochromatosis and Wilson disease (7). Hemochromatosis and Wilson disease are autosomal recessive disorders that result in accumulation of iron or copper levels that cause hepatic cellular injury, fibrosis, cirrhosis, oxidative stress, and formation of reactive aldehydes and mutations in cancer-related genes such as the *p53* tumor suppressor gene (11).

Chemical Toxins

Aflatoxins, toxic metabolites of the fungi *Aspergillus flavus* and *Aspergillus parasiticus*, are critical contributors to the development of HCC. These metabolites enter the human system by means of contaminated food, primarily grains (rice, wheat) in tropical and subtropical climates. Aflatoxins are enzymatically converted to aflatoxin B1 (AFB1) in the liver by cytochrome P-450 enzymes such as CYP3A4, CYP3A5, CYP3A7, and CYP1A2 (12). AFB1 is eventually converted into AFB1 formamidopyrimidine adduct, which is a potent carcinogen. The presence of AFB1 and its adducts in patients along with other critical liver disease contributors has been shown to increase the risk of HCC development (13).

The liver is the prime detoxifying organ and therefore is an important target for a number of chemical carcinogens. Compounds such as vinyl and polyvinyl chloride, Dithiothreitol, pyrethrins, chlordane, and polychlorinated biphenyls have been found to induce liver injury. Arsenic, a toxic metal found in contaminated ground water, is also known to have a potent effect in exacerbating liver injury (14). Industrial waste, such as organic solvents (aromatic, chlorinated, and alicyclic hydrocarbons) or trichloroethylene and perchloroethylene, can also lead to the development of HCC (15,16). These compounds can interact with nucleic acids and proteins, promoting a cancer-supporting molecular environment in the liver. Oxidation of these compounds is associated with the generation of reactive oxygen species. Acetaldehyde, a metabolic by-product of alcohol, is a potent inducer of oxidative stress, thereby exacerbating liver disease. Chronic alcohol abuse is known to exacerbate liver disease (17). These factors trigger signaling pathways leading to hepatic inflammation and the development of HCC.

Metabolic Syndromes

Metabolic syndromes, such as obesity, type 2 diabetes, and nonalcoholic fatty liver diseases, also increase a patient's risk of developing HCC (7,18). Insulin resistance leads to high free fatty acid flux, hyperglycemia, and hyperinsulinemia, all of which can cause fat accumulation, oxidative stress, profibrotic activities, and HCC (19). Hyperinsulinemia results in increased IGF1 and upregulation of the IGF1/insulin substrate 1 pathway, which contributes to the pathogenesis of HCC (20). Peroxisome proliferator-activated receptors also play an important role in the fatty liver and induction of carcinogenesis. Peroxisome proliferator-activated receptors regulate fatty acid uptake, the enzyme required for beta-oxidation of fatty acids and ketogenesis (21). Dietary as well as genetic obesity enhances interleukin (IL)-6 and tumor necrosis factor expression, leading to liver inflammation and tumorigenesis (22). Oxidative injury, endoplasmic reticulum stress, mitochondrial dysfunction, and apoptosis seen in HCC are caused by elevated levels of lipid peroxides and free radicals associated with metabolic syndrome (23).

CELLULAR AND MOLECULAR MECHANISMS OF HCC AND POTENTIAL THERAPEUTIC TARGETS

Inflammation/Immune System

Liver injury activates Kupffer cells, the resident macrophages of the liver. Activated Kupffer cells release cytokines and chemokines such as IL-6, tumor necrosis factor-α, IL-1β, T helper 1/T helper 2, and IL-12, resulting in inflammation (24,25). Inflammation in conjunction with