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Review

Biomarkers for virus-induced hepatocellular carcinoma (HCC)

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, and is advanced by severe viral hepatitis B or C (HBV or HCV) as well as alcoholic liver disease. Many patients with early disease are asymptomatic therefore HCC is frequently diagnosed late requiring costly surgical resection or transplantation. The available non-invasive detections systems are based on the clinical utility of alpha fetoprotein (AFP) measurement, together with ultrasound and other more sensitive imaging techniques. The hallmark of liver disease and its propensity to develop into fully blown HCC is depended on several factors including the host genetic make-up and immune responses. While common symptoms involve diarrhea, bone pain, dyspnea, intraperitoneal bleeding, obstructive jaundice, and paraneoplastic syndrome, the evolution of cell and immune markers is important to understand viral induced liver cancers in humans. The circulating miRNA, cell and immune based HCC biomarkers are imperative candidates to successfully develop strategies to restrain liver injury. The current molecular genetics and proteomic analysis have lead to the identification of number of key biomarkers for HCC for earlier diagnosis and more effective treatment of HCC patients. In this review article, we provide latest updates on the biomarkers of HBV or HCV-associated HCC and their co-evolutionary relationship with liver cancer.

Contents

Abbreviations: AFP, α-fetoprotein; HCC, hepatocellular carcinoma; HBV/HCV, Hepatitis B virus/C virus; DCP, des-gamma-carboxy prothrombin; GP73, Golgi protein; GPC3, Glypican-3; CD10, Cluster of differentiation 10; CD36, Cluster of differentiation 36; SAGE, serial analysis of gene expression; CALLA, common acute lymphatic leukemia antigen; LC–MS, liquid chromatography–mass spectrography; PIVKA-II, proteins induced by vitamin K absence; MMP, matrix metalloproteinase; 2D-PHAGE, 2-dimensional phage; MALDI-TOF, matrix-assisted laser desorption/ionization; SELDI-TOF, surface enhanced laser desorption/ionization time-of-flight; FNAB, fine needle aspiration biopsy; FNAC, fine needle aspiration cytology; FAT, fatty acid translocase; NAFLD, non-alcoholic fatty liver disease; CLD, chronic liver disease; CK7, Cytokeratin 7; CK19, Cytokeratin 19; NASH, nonalcoholic steatohepatitis; SFRP, secreted frizzled-related proteins; GRIPS, glypican-related integral membrane proteoglycans; ICC, intra hepatic cholangiocarcinoma; SCCA, squamous cell carcinoma antigen; FC-GP73, fucosylated GP73; GGT, γ-glutamyl transferase; AFU, α-1-fucosidase; TGF-β1, transforming growth factor-β1; HCR2, human carbonyl reductase 2 enzyme; GOLPH2, Golgi phosphoprotein 2; TSGF, tumor-specific growth factor; EGFR, epidermal growth factor receptor; EGF, epidermal growth factor; HGF, hepatocyte growth factor; FGF, fibroblast growth factor; TNF, tumor necrosis factor; IL-6, interleukin 6; DEN, diethylnitrosamine; STAT, signal transducer and activator of transcription; CXCR, N-terminal cysteines of CXC chemokines receptor; TH2, T-helper 2; VEGF, vascular endothelial growth factor; miR, miRNA; SCARB1, scavenger receptor class B member 1; SCARB2, scavenger receptor class B member 2; PTEN, phosphatase and tensin homolog; PDC4, pyruvate decarboxylase regulator 4; RECKS, reversion-inducing cysteines-rich protein with Kazal motifs.

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1. Introduction

Each year more than 500,000 new patients are diagnosed with hepatocellular carcinoma (HCC) in the world El-Serag, 2011. HCC is one of the fastest rising cancers in the region of China, Southeast Asia as well as Africa (Parkin et al., 2005). An overview of the basic understanding of epidemiology, stages and its multidisciplinary character of the disease is necessary to conquer the challenges faced in clinical research (Zoulim and Locarnini, 2012). It is the third most deadliest and fifth most common cancer across the world. HCC is a multi-factor, multi-step and complex process which occurs due to persistent infection of hepatitis B virus (HBV) and hepatitis C virus (HCV) (Kumar et al., 2003). Besides, usage of alcohol, aflatoxin B1 consumption is another etiological agent in HCC. The fatality rate is quite higher due to rapid tumor progression. In countries where hepatitis is not endemic, most of the HCC are not primary but metastasis of cancer from other parts of the body. Hepatitis is the inflammation of the liver caused by hepatitis virus. It can also be caused by other infections, toxic substances and autoimmune diseases. There are 6 different types of hepatitis viruses including A, B, C, D, E, and G, from which type A, B, and C are the most common. Hepatitis B is transmitted through blood and infected body fluid while hepatitis C virus is spread only through exposure to an infected person's blood (Mizejewski, 2001). Hepatic resection or transplantation is the only curative treatment available now for HCC patients (Mizejewski, 2001). Due to its asymptomatic nature, early detection of HCC is difficult and many patients present with advanced form of the disease at diagnosis and the prognosis for such patients remain poor. This review summarizes recent studies of potential biomarkers for diagnosis and to monitoring metastasis or recurrence of HCC.

2. HCC biomarkers

Biomarkers detectable in blood, urine, or tissue samples are used as molecular indicators for various types of diseases and their management. Their thresholds concentrations are used to detect the presence of various cofactors responsible for activating the diseases. Fluctuations in threshold concentrations have resulted in the prospective disease progression, diagnosis and guide therapy. Several biomarkers have been recognized for different diseases as well as research studies are still ongoing to fully understand and evaluate the clinical significance of utilizing such biomarkers. A lot of money and time can be saved as compared to empiric or other broad treatment approaches. Biomarkers could be more useful as a measurement tool to detect presence and progression of diseases, ultimately guiding them towards more targeted therapy. Understanding these markers is quite successful in detecting several type of cancer. They can also be used effectively in case of HCC. Molecular biomarkers were discovered using scientific platforms such as genomics along with proteomics. Fig. 1 depicts the various pathways activated when HCC is induced. Apart from genomics and proteomics platforms, biomarker assay techniques such as glycomics, metabolomics, secretomics and lipidomics are the most commonly used as techniques in identification of biomarkers. Northern blot, Gene expression, SAGE and DNA Microarray, Proteomic Approach involves 2D-PAGE, LC–MS, SELDI-TOF (or MALDI-TOF), Ab Microarray and Tissue Microarray are involved to develop the screening of biomarkers at various grades of the disease.

2.1. Protein biomarkers

2.1.1. Alpha fetoprotein (AFP)

For decades, the most commonly used biochemical blood test to detect liver cancer is by screening for alpha fetoprotein (AFP). AFP is a glycoprotein with a molecular weight of 70 kDa, secreted by immature fetal liver cells and appears in cancer cells. AFP acts as a transporter molecule for several ligands, such as fatty acids, phytoestrogen, heavy metals, retinoid, steroids, flavonoids, dyes, bilirubin, dioxin and various drugs (Mizejewski, 2001). AFP is thought to exhibit immunosuppressive activity; as it plays a vital role in regulation of cell proliferation (O'Neill et al., 1982). This plasma protein is synthesized by yolk sac and by the liver. It is one of the chief proteins secreted during the fetus development and is present in very low levels in adults. Therefore AFP is one of the several tumor markers that are present at high level when a person is affected by cancer. It is mainly found in nonseminomatous germ cell tumor and in liver cancer. Patients with cirrhosis or chronic hepatitis also are reported with higher blood levels of alpha-feto protein (Fattovich et al., 2004). The level of AFP is higher in early stages of HCC, but it normalizes as disease progresses (Llovet et al., 2008). In general, it has been indicated serum AFP level more than 500 ng/mL, indicating the presence of HCC but

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