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Paraneoplastic Syndromes in Hepatocellular Carcinoma: Epidemiology and Prognosis

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Abstract

In terms of prevalence, hepatocellular carcinoma (HCC) is the seventh most frequent malignancy worldwide. East and Southeast Asia as well as sub-Saharan Africa are high-risk areas. Men experience rates that are at least two to three times higher than women, regardless of ethnicity or location; this sex ratio is more prominent in high-risk areas. Over the past 20 years, HCC rates in the US have climbed by 70%. Similar trends can be seen in registry data from Canada and Western Europe. In contrast, the prevalence of HCC has steadily decreased over the past 20 years in Singapore and Shanghai, China, both high-risk areas. The frequency of HCC is inversely related to socioeconomic class position among both white and black Americans. The hepatitis B virus (HBV) infection is by far the most significant risk factor for HCC in humans. According to estimates, HBV has a causal role in 80% of HCC cases worldwide. HBV is thought to be responsible for one in four instances of HCC among non-Asians in the United States, despite the low overall infection incidence. Hepatitis C virus infection is thought to have a relatively little impact on the development of HCC in Africa and Asia, despite being a significant risk factor for HCC in the United States. In portions of Asia and Africa, dietary aflatoxin exposure is a significant codeterminant of the risk of HCC. Excessive alcohol use, cigarette smoking, and female oral contraceptive use are risk factors for HCC in both Canada and the US.

Keywords: Epidemiology; Hepatocellular Carcinoma; Hepatitis C; Virus infection

Introduction

The fifth most frequent type of cancer worldwide, hepatocellular carcinoma (HCC) is associated with a high fatality rate. Patients with symptomatic HCC frequently have constitutional symptoms in addition to abdominal pain or a mass in addition to lethargy, anorexia, and weight loss. Patients may occasionally have unusual features as a result of paraneoplastic symptoms of HCC. Hypercholesterolemia, hypercalcemia, erythrocytosis, hypoglycemia, demyelinating illness, pemphigus, polyarthritis, encephalomyelitis, and thrombocytosis are among the paraneoplastic syndromes (PNS) that have been linked to HCC. Hypercholesterolemia, hypercalcemia, hypoglycemia, and erythrocytosis are the most typical PNS linked to HCC [1].

There is not a lot of research on PNS in HCC. According to earlier research, HCC patients with PNS have more advanced disease, higher levels of the protein alpha-fetoprotein (AFP), and worse survival rates than those without. PNS was revealed to be an independent, unfavourable prognostic factor for survival in a study of PNS in patients with HCC conducted in Taiwan. It is yet unclear, though, if a specific PNS is linked to a noticeably worse outcome than others or whether all PNS have a similar impact on it. It is well established that hepatocyte lipid metabolism and hepatitis C virus (HCV) infection are tightly related. According to a recent study, cholesterol and FA synthesis increased without any negative feedback, indicating that the lipid metabolism in the liver of people with HCV infection was dysregulated. In nonalcoholic steatohepatitis (NASH), glucose and lipid metabolism are dysregulated from the beginning of NASH and remain so throughout the entire oncogenic stages. Furthermore, a recent study found that precancerous cirrhotic livers have amplified gene expression of glycolytic enzymes, which is strongly linked to an increased risk of developing HCC [2].

Moreover, HCC is known to alter its pathological characteristics according to the level of differentiation. One of them, well-differentiated HCC, is recognised as a fat-containing tumour, and the accumulated fat evaporates when the level of differentiation decreases to moderate or poor. Although it is assumed that reduced portal vein flow and inadequate arterial development is the root causes of this fatty alteration in early-stage HCC tissue, examples of hyper vascular HCCs containing intracellular fat do occasionally occur in clinical practise. The metabolic profile of well-differentiated HCC and metabolic change as the degree of differentiation worsens are still not well understood at this time [3].

Here, we looked at the metabolic enzyme gene expression levels in malignant and non-cancerous tissues from human HCC samples. We also looked at the expression as liver disease progressed from a healthy liver to cirrhosis, chronic hepatitis, and HCC. In addition, to confirm that the results of the gene expression studies are indeed connected to metabolomics, we did metabolomics analysis utilising the NASH-HCC mouse model. In order to better understand the process of lipid droplet accumulation in well-differentiated HCC, we also analysed the metabolic gene expressions by the levels of HCC differentiation.

Alpha-fetoprotein (AFP) and ultrasounds every 6 to 12 months are currently the gold standard and most often utilised indicators for patients at risk for HCC; however they are far from ideal. More than 400 ng/mL of serum AFP is considered diagnostic, however only a tiny subset of patients with HCC have such high values. Due to limitations in recall techniques, ultrasound surveillance, even when conducted every three months, cannot enhance detection of tiny HCC [4].

The role of biomarkers related to early detection, invasiveness,

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metastasis, and recurrence has attracted significant research interest due to advancements in tumour biology and the development of cellular and molecular techniques, leading to the discovery and use of several novel markers in this disease. In this essay, we want to provide a summary of the data that are currently accessible in this rapidly developing field of study [5].

Materials and Methods

103 HCC patients who had hepatic resection at Kyushu University Hospital provided tissue samples, both malignant and non-cancerous. Two leading liver pathologists assigned each HCC's pathologic differentiation grade. Twelve living liver transplant donors who had normal histology findings and liver function were used as controls to get normal liver tissues. Written consent was obtained before the study was authorised by the ethics committee of Kyushu University Hospital (numbers 29-403 and 30-35) [6].

We bought male C57BL/6J wild-type (WT) mice from Japan SLC (Shizuoka, Japan). The C57BL/6J-based melanocortin-4 receptor-deficient (MC4R-KO) mice were a kind gift from Dr. Joel K. Elmquist (University of Texas South-western Medical Center). Unless where stated, all animals were provided with free access to water and a normal meal (CE-2; 343.1 kcal/100 g, 12.6% energy as fat; CLEA Japan) while being habituated to their surroundings in a temperature-, humidity-, and light-controlled room (12 h light and 12 h dark cycle). Male MC4R-KO mice aged 8 weeks were fed the western diet (D12079 B; 468 kcal/100 g, 41% calories as fat, 34.0% sucrose, 0.21% cholesterol; Research Diets, New Brunswick, NJ) for 60 weeks, whereas male WT mice served as the control group and received the standard diet. All of the animals were put to sleep with isoflurane at the conclusion of the experiment, and their livers were removed and promptly frozen in liquid nitrogen for mRNA extraction and metabolomics analysis. The Animal Care Committee of Kyushu University gave its approval to all investigations, which were carried out in accordance with the National Institutes of Health's Handbook for the Care and Use of Laboratory Animals [7].

Discussion

Hepatocarcinogenesis is a multistate, complex process that often starts after years of prolonged exposure to a variety of mutagenic and mutagenic settings that cause random genetic changes. According to recent research, the proliferation and invasiveness of a tumour's inherent biologic properties are likely related to the microenvironment's composition and activity, which has a significant impact on the tumour's clinical course. The ability of HCC to generate a variety of tumor-related proteins sets it apart from other cancers and makes it more appropriate for biomarker-related study. Selecting the biomarkers that would be most helpful in clinical practise has proven to be difficult due to the high number of biomarkers that have been reported in this condition. We made an effort to concentrate on the most commonly used and acknowledged biomarkers in this pretty succinct summary [8].

Serum AFP is still the most frequently used tumour marker in clinical practise, despite its drawbacks. Current studies show that in order to distinguish HCC from non-malignant hepatopathy and detect tiny HCC, AFP-L3 and DCP, two circulating AFP subtractions unique to hepatoma, perform better than AFP alone. In addition, it has been demonstrated that various additional tumour markers, including as GPC3, GGT II, and AFU, can be used in addition to AFP and DCP to detect HCC. Some of them can even be found in HCC patients who are seronegative for both AFP and DCP, suggesting that the accuracy may be increased by determining these markers simultaneously [9].

The discovery of a novel class of molecules known as miRNAs, however, has been the most fascinating and promising field of research into this disease. MiRNAs have been found to be abnormally expressed in HCC, and several of them have been linked to the development and progression of the cancer. Moreover, several microRNAs are linked to HCC or connected to HCC subtypes, suggesting the potential utility of microRNAs in the diagnostic and prognostic stratification of HCC patients. These HCC-associated miRNAs have some of their validity shown in several cohorts. With the ultimate goal of individualised therapy, this opens up the possibility of creating clinically practical platforms for HCC diagnosis, risk assessment, and patient risk stratification [10].

Conclusion

Many biomarkers that could supplement information obtained from conventional histopathological features for HCC biologic behaviour, metastasis, and recurrence have been discovered as a result of research into the molecular biology of hepatocarcinogenesis. Many biomarkers have been demonstrated to have potential predictive value. Nonetheless, the most of these have been researched in the past. Prospective clinical trials should be the focus of efforts when analysing the prognostic importance of these markers. These molecules not only aid in predicting the prognosis for HCC patients, but they may also help choose the best therapy modality and serve as brand-new targets for therapeutic interventions.

Acknowledgement

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Conflict of Interest

None

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