Hepatobiliary & Pancreatic Diseases International 18 (2019) 493–494

Contents lists available at ScienceDirect

Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd

Viewpoint

Food for thought on hepatocellular carcinoma

Miao Fang[a], Min Yao[b], Li Wang[a], Deng-Fu Yao[a,*]

[a] Research Center of Clinical Medicine, Affiliated Hospital of Nantong University, Nantong 226001, China
[b] Department of Immunology, Medical School of Nantong University, Nantong 226001, China

Hepatocellular carcinoma (HCC) is a serious public health problem worldwide [1]. Recently, Chen et al. [2] reported the observed survival and relative survival of leading cancer sites from a population-based cancer registry for 40 years in the inshore areas of the Yangtze River. HCC ranks the first among all malignancies and the poorest survival rate among cancer types in Qidong, China. The data indicated that the prevention and treatment of HCC still are far from satisfaction.

Recently, Yang et al. [3] reported that the long-term intake of whole grains/dietary fiber reduces the risk of adult HCC. The prevention of HCC is the most promising strategy in reducing its incidence and mortality. Emerging evidences indicate that numerous nutrients and nonnutrient dietary bioactive components reduce the incidence and/or delay HCC development through modifications of deregulated epigenetic mechanisms [4]. However, the pathogenesis of HCC is poorly understood. Future studies on the effects of whole grain/dietary fiber intake on patients with HBV/HCV infection, on different racial/ethnic or high-risk populations are needed to elucidate the exact underlying mechanisms [3].

The leading etiological factors of HCC include chronic HBV or HCV infection [5], aflatoxin B1 (AFB1) contaminated food intake, alcohol consumption, non-alcohol fat liver diseases (NAFLD), metabolic disorders, and other environmental factors. Recent advances in genomics provide insight into the mechanisms of HCC [6]. Chronic HBV carriers have a 5- to 15-fold increased risk of HCC compared with the general population. HBV/HCV infections represent a major global public health and economic burden, with an estimated 257 million and 71 million people, respectively, worldwide. The natural history of HBV or HCV in children depends on age at time of infection, mode of acquisition, ethnicity, and genotype [7]. Most children infected perinatally or vertically remain asymptomatic but are at uniquely higher risk of developing chronic hepatocytes damage, progressing to liver cirrhosis and HCC, hence classifying HBV/HCV as oncoviruses. The representative data on epidemiology of HCC is scarce and cancer is not a reportable disease and the cancer registries are mostly urban. Accumulating basic and clinical data suggested that HBV/HCV infection still is considered an important etiology of HCC [7].

The high whole grain/dietary fiber intake is beneficial to prevention of HCC. However, the avoidance of AFB1 contaminated food intake was of great importance. The evidence for AFB1-induced epigenetic alterations with potential mechanisms involved in HCC development. AFB1 is currently the most commonly studied mycotoxin due to its great toxicity and its distribution in a wide variety of foods such as grains and cereals. The genetic modifications begin in the liver through the biomorphic AFB1, the AFB1-exo-8.9-Epoxy active, which interacts with DNA to form adducts of AFB1-DNA, inducing mutation in codon 249, mediated by a transversion of G-T in the p53 tumor suppressor gene in hepatocarcinogenesis [8]. AFB1 interact synergistically with HBV/HCV infection or alcohol consumption leading to vert liver cirrhosis is the predominant risk factor for HCC development. Prevention of viral infection by universal vaccination against hepatitis virus, HCC surveillance program, preventing alcoholic liver diseases, fungal contamination of grains and ground crops to prevent basically AFB1 exposure are important measures to prevent hepatocytes damage or malignant transformation through genetic and epigenetic modifications.

Alterations of hepatic metabolism are critical to the development of liver disease. Now, the incidence of NAFLD among healthy populations is increasing and has become one of the most common causes of liver disease worldwide [9,10]. NAFLD characterized by liver fat accumulation affects at least 30% of the global population and has recently been recognized as an important etiology contributing to the increased incidence of HCC. The more aggressive form, nonalcoholic steatohepatitis (NASH), is characterized by hepatocyte necrosis and inflammation. The development of effective approaches for disease prevention and/or treatment heavily relies on deep understanding of the mechanisms underlying NAFLD to HCC development [11,12]. An accumulation of ectopic fat, including visceral obesity and fatty liver leads to a dysfunction of the adipose tissue with impaired production of adipocytokines, inactivity of carnitine palmitoyl transferase II located on the mitochondrial inner membrane [13], and the presence of NAFLD resulting in the emergence of a microenvironment favorable to HCC development. However, it was worthy to explore how decreasing liver fat accumulation and further understanding the molecular mechanisms involved in the cascade of NAFLD to HCC progression.

Although HCC as an aggressive and life-threatening disease often was diagnosed at intermediate or advanced stages, which substantially limits approaches to its effective treatment. HCC

* Corresponding author.
E-mail address: yaodf@ahnmc.com (D.-F. Yao).

https://doi.org/10.1016/j.hbpd.2019.04.010

progression with chronic constant hepatocyte damage or hepatic microenvironment resulted in the generation of an oncogenic microenvironment, creating a prooncogenic milieu and thus promoting hepatocyte transformation. Recently, cellular and molecular studies have shown that adult hepatocytes are the cells of original liver tumors, with different possible pathways in hepatocarcinogenesis. Genetic analyses from HCC tissues have provided important information about tumor initiation and progression. Genomic classification of HCCs based on their molecular features has led to new treatments for HCC [14]. Multi-kinase inhibitors except of sorafenib have been approved for HCC treatment, and the preliminary success of immunotherapy has raised hopes. New knowledge of these findings could help unravel the HCC pathogenesis to devise new prevention strategies and a potentially be used to individualize HCC management.

Contributors

YDF proposed the study. FM, YM and WL wrote the manuscript. YDF is the guarantor.

Funding

This study was supported in part by grants-in-aid from the Science and Technology Project of Nantong City (MS12017014-4), and the Science and Technology Project of Jiangsu Province (BE2016698).

Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

[1] Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. Gastroenterology 2019;156:477–491.
[2] Chen JG, Zhu J, Zhang YH, Zhang YX, Yao DF, Chen YS, et al. Cancer survival in Qidong between 1972 and 2011: a population-based analysis. Mol Clin Oncol 2017;6:944–954.
[3] Yang W, Ma Y, Liu Y, Smith-Warner SA, Simon TG, Chong DQ, et al. Association of intake of whole grains and dietary fiber with risk of hepatocellular carcinoma in US Adults. JAMA Oncol 2019. doi:10.1001/jamaoncol.2018.7159.
[4] Moreno FS, Heidor R, Pogribny IP. Nutritional epigenetics and the prevention of hepatocellular carcinoma with bioactive food constituents. Nutr Cancer 2016;68:719–733.
[5] Mysore KR, Leung DH. Hepatitis B and C. Clin Liver Dis, 2018;22:703–722.
[6] Chaturvedi VK, Singh A, Dubey SK, Hetta HF, John J, Singh MP. Molecular mechanistic insight of hepatitis B virus mediated hepatocellular carcinoma. Microb Pathog 2019;128:184–194.
[7] Kar P. Risk factors for hepatocellular carcinoma in India. J Clin Exp Hepatol 2014;4:S34–S42.
[8] Ferreira RG, Cardoso MV, de Souza Furtado KM, Espíndola KMM, Amorim RP, Monteiro MC. Epigenetic alterations caused by aflatoxin b1: a public health risk in the induction of hepatocellular carcinoma. Transl Res 2019;204:51–71.
[9] Brandi G, De Lorenzo S, Candela M, Pantaleo MA, Bellentani S, Tovoli F, et al. Microbiota, NASH, HCC and the potential role of probiotics. Carcinogenesis 2017;38:231–240.
[10] Divella R, Mazzocca A, Daniele A, Sabbà C, Paradiso A. Obesity, nonalcoholic fatty liver disease and adipocytokines network in promotion of cancer. Int J Biol Sci 2019;15:610–616.
[11] Piccinin E, Villani G, Moschetta A. Metabolic aspects in NAFLD, NASH and hepatocellular carcinoma: the role of PGC1 coactivators. Nat Rev Gastroenterol Hepatol 2019;16:160–174.
[12] Chen K, Ma J, Jia X, Ai W, Ma Z, Pan Q. Advancing the understanding of NAFLD to hepatocellular carcinoma development: from experimental models to humans. Biochim Biophys Acta Rev Cancer 2019;1871:117–125.
[13] Gu JJ, Yao M, Cai Y, Fang M, Wang L, Zheng WJ, et al. Dynamic expression of carnitine palmitoyltransferase II in the mitochondrial inner membrane during hepatocyte malignant transformation induced by lipid accumulation. Zhonghua Gan Zang Bing Za Zhi 2017;25:279–284.
[14] Dhanasekaran R, Nault JC, Roberts LR, Zucman-Rossi J. Genomic medicine and implications for hepatocellular carcinoma prevention and therapy. Gastroenterology 2019;156:492–509.

Received 12 March 2019
Accepted 9 April 2019
Available online 24 April 2019