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Mini-review

Heterogeneity of liver cancer and personalized therapy

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ABSTRACT

Liver cancer is an extraordinarily heterogeneous malignant disease among the tumors that have so far been identified. Hepatocellular carcinoma (HCC) arises most frequently in the setting of chronic liver inflammation and fibrosis, and takes a variety of course in individual patients to process to tumor. The risk factors such as HBV and/or HCV infections, aflatoxin infection, abuse alcohol intake, metabolic syndrome, obesity and diabetes are closely related to the environmental and genetic susceptibilities to HCC. The consequent resulting genomic instability, molecular and signal transduction network disorders and microenvironmental discrepancies are characterized by the extraordinary heterogeneity of liver cancer. The histology-based definition of the morphological heterogeneity of liver cancer has been modified and refined to treat patients with targeted therapies, but this still cannot solve all the problems. Lack of consistent outcome for anticancer agents and conventional therapies in liver cancer treatment calls for assessing the benefits of new molecularly targeted drugs and combined therapy, under the heterogeneity condition of tumor. The present review article will provide the complex mechanism and phenotype of liver cancer heterogeneity, and help us to execute precision medicine in a really personalized manner.

Introduction

As the proverb goes, every coin has two sides. Heterogeneity, an old word from ancient Greece, has its good aspects and bad ones. Heterogeneity exists in every corner of the universe, from atomic level to planet level, and from material perspective to spiritual perspective. The heterogeneity of species from Darwinian evolutionary theory keeps the balance of ecological environment on the earth. Ethnic heterogeneity contributes to the diversity of culture. But in the tumor world, one of the most formidable enemies of humankind, its heterogeneity presents formidable challenges to understanding of the diseases and designing effective treatment strategies.

Morphological tumor heterogeneity was first documented by pathologists in the 1890s [1]. In the late twentieth century, the clonal origin and stepwise progression of tumors was convincingly expounded. A revolutionary insight on tumor heterogeneity proposed by Peter Nowell et al. that tumors caused by multiple mutations or "hits" precipitate certain clones to grow through the accumulation and selection of genetic changes, resulting in advanced tumors being highly individualized, which in turn may require individualized treatment [2]. Contemporarily, Fidler and Kripke evidenced that malignant melanoma cells from one parent tumor varied from each other in terms of metastatic colony formation ability within the lung [3]. Similarly, Heppner et al. isolated four cell lines from a single autochthonous BALB/cfC3H mammary tumor using a variety of cell culture and separation methods. These lines differed significantly from each other in morphology, growth properties, karyotype and the expression of murine mammary tumor virus antigen [4]. Recently, the rapid progress of molecular biotechnologies, such as the next generation sequence and CRISPR/Cas9, demonstrated tremendous potential on the molecular studies and clinical translational implications of tumor heterogeneity.

Liver cancer ranks the second leading cause of cancer-related mortality in man in developing countries and the sixth in developed countries. Hepatocellular carcinoma (HCC) has been the most prevalent malignant neoplasm of the liver, and cholangiocarcinomas, derived from the epithelial lining of the bile duct, have been rarely found. A total of 782,500 new cases of liver cancer and 745,500 death cases occurred worldwide, of which China alone accounted for about 50% [5]. Liver cancer, one of the extraordinarily heterogeneous diseases, has become a serious social and medicine issue. In this review, we summarize the etiology and the inter- and intra-phenotypes of liver cancer heterogeneity, and discuss what clues can be drawn for tumor biology and personalized therapy.

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Environmental and genetic susceptibilities

HCC arises most frequently in the setting of chronic liver inflammation and fibrosis due to viral infections, metabolic injuries, toxic insults, or autoimmune reactions [6]. Among the tumors that so far have been documented, HCC presents one of the closest relationships between an environmental agent and a tumor [7]. The variable natural history, extraordinarily multiple environmental susceptibilities, and individual genetic predisposition to HCC are characterized by the high heterogeneity of the tumor.

Around 80% of HCCs were involved with HBV and/or HCV infections. The proportion of etiological factors of HCC in the United States, Europe, Egypt and Japan is as follows: HCV accounting for more than 60%, HBV for about 20%, and chronic alcoholism and other factors for about 20%. In Africa and Asia the proportion is: HBV for 60%, HCV for 20%, chronic alcoholism and aflatoxin infection and other factors for 20% [7]. About 2 billion people have been infected with HBV, and over 350 million have become chronic carriers [8]. The risk of developing HCC is 10–100 fold in carriers with chronic liver disease (CLD) compared with uninfected people [9,10]. In China, HCC with HBV infection has been found to be closely associated with development of portal vein tumor thrombus (PVTT) and worse outcome [11]. Up to 85% of acute infections with HCV become chronic infections, of which 50% progress to CLD, of which 5–20% develop cirrhosis and of which 1–2% suffer HCC per year [12].

Studies in the United States and Italy suggest that alcohol is the most common cause of HCC. More than 18 million adults in the US abuse alcohol or consume greater than 80 g per day for 10 years, which increases the risk for HCC above 5-fold. The risk for HCC in decompensated alcohol induced cirrhosis approaches 1% per year. Alcohol use in chronic hepatitis C doubles the risk for HCC as compared with the risk in hepatitis C alone [13]. In Taiwan, heavy alcohol consumption was reported to significantly increase the risk of HCC in HBV-related cirrhotic patients [14]. The epidemic of overweight and metabolic syndrome has emerged as a relevant risk factor for HCC [15]. Non-alcoholic fatty liver disease (NAFLD), closely associated with metabolic syndrome, obesity and diabetes, is considered to be the most common liver disorder in developed countries, and has been increasingly diagnosed worldwide. Simple steatosis is benign, whereas non-alcoholic steatohepatitis (NASH) can lead to cirrhosis, liver failure and HCC [16]. Around 7% of patients with compensated NAFLD-related cirrhosis, compared with cirrhosis associated with alcohol or HCV, will develop HCC within 10 years [17]. As expected, cigarette smoking has been causally associated with the risk of HCC [18].

Note that the etiology of intrahepatic cholangiocarcinoma (ICC) has not been clearly understood. Only 10% of ICC has been verified to result from chronic inflammation [19], and its associations with HBV or HCV infection and alcohol consumption may also exist, but are not well corroborated [20,21]. Nevertheless, relatively strong associations have been documented with primary sclerosing cholangitis (PSC) [21], liver fluke infestations and hepatolithiasis [22–24].

Genomic instability is a primary source of genetic diversity which generates diverse cell populations and inter- and intra-tumor heterogeneities [25]. Most tumor types exhibit increased occurrence of genomic instability in stepwise progression. In HCC, the viral etiological factors, including reactive oxidative, nitroxidative species by the tumor microenvironment, inactivation of detoxification systems, telomere shortening, DNA methylation and replication stress, all contribute to genomic instability [26]. The chromosomal instability (CIN) stands out as the predominant form of genomic instability, whereas microsatellite instability (MSI) shows rarely in HCC [27]. Human HCC has now been divided into two major subgroups in terms of genomic stability: firstly, the β-catenin mutations and chromosome 8p losses; secondly, frequent allelic losses on chromosomes 1p, 4q, 6q, 9p, 13q, 16p, 16q, and 17p associated with p53 and *AXIN1* mutations [28]. Similarly, in transgenic mouse models, two distinct patterns of genomic instability were determined. A low rate of genomic instability but a frequently activated Wnt/β-catenin pathway was found in c-Myc and c-Myc/E2F1 transgenic mice. Conversely, a high rate of genomic instability accompanies rarely activation of Wnt/β-catenin was found in co-expression of c-Myc and TGF-α transgenic mouse [29]. A kinetic model was recently established to assess the genetic alterations occurring in liver cancers developed in diethylnitrosamine (DEN) treated mice [30]. By checking different time-points of DEN induced generation of liver cancer, Michael R. Speicher et al. found that chromosomal gains and losses were early observed in week 32 and increased significantly in week 56. Moreover, the loss of distal chromosome 4q, which contained several HCC suppressor genes such as Runx3 [31] and Nr0b2/Shp [32], occurred early and persisted during all tumor stages. Intriguingly, the mutations and activation of Wnt/β-catenin occurred at late stages, but were not involved in tumor initiation in this model.

Morphological heterogeneity

Liver cancer is defined as an extraordinarily heterogeneous disease due to its morphological diversity. The histology-based definition of the morphological heterogeneity of liver cancer has been modified and refined again and again over time, in an effort to treat patients with personalized therapies, and has provided a more precise prognosis for doctors. The primary liver cancers classified by the World Health Organization (WHO) are primary HCC, ICC, and combined hepatocellular and cholangiocarcinoma (cHCC-CC) [33]. The common histological types of HCC defined by WHO are thin trabecular type, thick trabecular type, pseudoglandular type, and compact type, etc. The cellular phenotypes of HCC are as follows: clear cell type, fat-rich type, spindle cell type, undifferentiated type, etc. ICC has been the second most common type of primary liver cancer, and adenocarcinoma is the main type with many other specific histological and cytological types. The incidence of cHCC-CC has been ranging from 1.0 to 14.2% [34]. The histological feature of cHCC-CC covers the presence of a mixture of both distinct canonical HCC and ICC components within a single nodule, with each one maintaining its own histochemical phenotype. Another novel subtype of HCC is pathologist named dual-phenotype HCC (DPHCC), which is different from cHCC-CC and recognized as a typical morphological HCC strongly co-expressing both hepatocyte and cholangiocyte markers within the same tumor cells. DPHCC behaves differently from classical HCC with relatively high malignancy [35].

The morphological heterogeneity of liver cancer has also been demonstrating itself in tumor differentiation status, tumor growth patterns and pathological features of paratumor tissues [33]. HCCs were classified as well differentiated, moderately differentiated, poorly differentiated, and undifferentiated according to their differentiation degrees. Tumor growth patterns include invasion of ambient normal liver tissue, invasion of capsule, generation of satellite nodules, intrahepatic metastasis, and formation of tumor thrombi. Also accounting for tumor heterogeneity, the inflammation grade (G) and fibrosis stage (S) in the surrounding tissues of tumor were classified from G1 to G4 and S0 to S4.

Molecular and signaling network disorders

Under the environmental and genetic “hits” of the clonal evolution model, studies on oncogenic events at the molecular and signal transduction network, phylogenetic analysis, and epidemiologic studies to identify major risk factors for HCC and ICC are important to understand the mechanism of tumor heterogeneity and accomplish personalized treatment.

The HBV gene product hepatitis B virus X protein (HBx) serves as a multifunctional viral regulator. It is considered as one of the