Cancer Letters xxx (2017) 1–6

Contents lists available at ScienceDirect

Cancer Letters

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

Mini-review

Precision diagnosis and treatment of liver cancer in China

Jing Fu [a, b], Hongyang Wang [a, b, *]

[a] International Co-operation Laboratory on Signal Transduction, Eastern Hepatobiliary Surgery Institute, Second Military Medical University, Shanghai 200438, China
[b] National Center for Liver Cancer, Shanghai, China

ARTICLE INFO

Article history:
Received 3 August 2017
Received in revised form
9 October 2017
Accepted 9 October 2017

Keywords:
Liver cancer
Hepatocellular carcinoma
Early diagnosis
Personalized therapy

ABSTRACT

Liver cancer ranks the sixth in cancer incidence and the second in tumor related mortality worldwide, with over half of the new cases and deaths occur in China. Because of difficulties in early diagnosis, rapid progression and lack of targeted drugs, the survival rate of liver cancer is extremely low. The existence of extraordinary heterogeneity has greatly limited the progress in early detection, molecular classification and targeted therapy of live cancer, owing to its varied risk factors, genetic susceptibilities, morphological diversity and microenvironmental discrepancies. Based on the heterogeneity of individual patients, precision medicine brings a new dimension to cancer personalized diagnosis and more-targeted treatment, and even give us access to pre-clinical screening of tumors in high risk populations. The present review article will provide progresses in precision diagnosis, molecular classification, signaling dis-regulation, preclinical models and personalized treatment of liver cancer in China.

Introduction

Liver cancer is the sixth most diagnosed cancer and the second leading cause of cancer death worldwide [1]. China alone accounts for over half of the new cases and deaths, with 466,100 new cases and 422,100 deaths in 2015 [2]. Most (70%–90%) common type of primary liver cancers are hepatocellular carcinoma (HCC) [1]. Among all cancers in China, the liver cancer has the poorest survival—the age-standardized 5-year relative survival is only 10.1% [3]. This is mainly because of difficulties in early diagnosis, leading to most liver cancer patients are diagnosed at an advanced stage, especially in China. Moreover, being highly malignant with rapid progression, the treatment for advanced liver cancer is difficult and the therapeutic effect is usually poor due to the low selectivity and toxicity of chemotherapy drugs.

Liver cancer is one of the extraordinarily heterogeneous diseases, owing to its highly heterogeneous risk factors, environmental or genetic susceptibilities, morphological diversity, signaling network disorders and microenvironmental discrepancies [4–6]. The existence of individual heterogeneity has greatly limited the progress in early detection, molecular classification and targeted therapy of live cancer. Precision medicine promises strategy for the prevention and treatment of tumors, which is based on the heterogeneity of individual patients [7,8]. By harnessing huge amounts of clinical data, from multi-omic data to health records, precision medicine bring a new dimension to cancer personalized diagnosis and more-targeted treatment, and even give us access to pre-clinical screening of tumors in high risk populations. In this review, we summarize the progresses in precision diagnosis and treatment of liver cancer in China.

Early diagnosis and molecular classification

The majority of HCC patients are diagnosed at a late stage at which it is too far advanced to be cured [9]. The key challenge in HCC control and prevention is to detect of the disease as early as possible, which provides a tremendous opportunity to improve the outcome for people with HCC [10–12].

A combination of ultrasound imaging (US), computer tomography (CT) imaging, magnetic resonance imaging (MRI) and measurement of serum alpha-fetoprotein (AFP) levels has been the major traditional method for diagnosing and screening HCC [13]. Improved imaging techniques have made ultrasound possible to detect small liver lesions, but it highly depends on the operator's experience and is limited in its ability to differentiate HCC from benign nodules [14–16]. Measuring serum AFP concentration has been one of the conventionally used methods for HCC diagnosis,

* Corresponding author. International Cooperation Laboratory on Signal Transduction, Eastern Hepatobiliary Surgery Institute, The Second Military Medical University, 225 Changhai Road, Shanghai 200438, China.
E-mail address: hywangk@vip.sina.com (H. Wang).

https://doi.org/10.1016/j.canlet.2017.10.008
0304-3835/

since FDA approval in the 1980s. Trevisani et al. suggested the best cut-off for AFP ranges from 16 to 20 ng/ml , with the specificity and sensitivity were 90% and 60%, respectively [17]. That means a considerable number of patients with HCC would be missed at this threshold [18,19]. Although AFP was more sensitive than des-γcarboxy-prothrombin and lectin-bound AFP (AFP-L3%) for the diagnosis of early and very early stage HCC , it has only 66% sensitivity with a new cutoff of 10.9 ng/ml [20]. Eighty percent of the cases of small HCC showed no increased serum AFP concentration, and the sensitivity of AFP even decreased from 52% towards 25% when the tumor diameter is <3 cm [21]. About 10%–43% patients with chronic HCV [22,23], 15%–51% patients with chronic HBV [24,25], liver cirrhosis or other liver diseases also have raised AFP levels. Furthermore, AFP has not been utilized as the independent screening biomarker among high-risk populations for developing HCC (AASLD practical guidelines in 2010 and NCCN clinical practice guidelines in 2015) due to its poor sensitivity and specificity.

It has been reported in recent years that Glypican-3 (GPC3), Dickkopf-1 (DKK1) and circulating miRNAs, could serve as candidate biomarkers for early HCC [26–28]. Glypican-3 (GPC3, named also MXR7) belongs to the glypican family of Glycosylphosphatidylinositol (GPI)-anchored heparan sulphate proteoglycans (HSPGs) [29]. GPC3 is specifically overexpressed in most HCC tissues and elevated in the serum of a large proportion of HCC patients, reported by our group and others [30–33]. Regarding the early detection of HCC in liver cirrhosis, frequency of GPC3 overexpression was significantly higher than that of an elevated serum level and mRNA level of AFP in small HCC [30]. Further more, immunostaining for GPC3 was very helpful in distinguishing early and grade-1 HCC from dysplastic nodules arising in cirrhosis, suggesting GPC3 as a tissue marker for the early detection of HCC [34].Our group identified the monoclonal antibodies, which can strongly bind the nature form of GPC3, and then developed the Glypican 3 Detection Kit for HCC diagnosis. This is the first pathological detection kit for HCC with complete intellectual property in China issued by China Food & Drug Administration (CFDA) in 2014. Further analysis is needed to evaluate the usefulness of candidate biomarkers in routine pathological diagnosis including biopsy diagnosis and, more importantly, as serum markers for early detection of HCC.

Circulating miRNAs have unique expression patterns in various tumors including HCC [28,35,36], implying their promising prospects as pre-clinical screening biomarkers. Recently, a seven-center retrospective longitudinal study in China was conducted to identify serum miRNAs biomarkers for HCC pre-clinical screening, as part of the National Cancer Institute's Early Detection Research Network (EDRN)-defined phase 3 study [37]. A set of serum miRNAs including miR-193a-3p, miR-369-5p, miR-672, miR-429 and let-7i* were identified in pre-clinical HCC patients and have the potential to screen for CHB patients at high risk to develop HCC 6–12 months after miRNAs measurement. These circulating miRNAs, as non-invasive biomarkers, combined with the conventional screening tools using AFP and ultrasound, may have great promise for the prediction and prevention of HCC in high-risk populations [38].

In most human malignancies including HCC, clinical classification plays an essential role in prognosis assessment and treatment design. Considerable efforts have been made to obtain a refined molecular classification of HCC [39–41], but the major challenge still remains due to the overwhelming genomic complexity of HCC. Fortunately, recent progress in systems biology shed new light on HCC biomarker screening and validation. Application and integration of high throughput screening technology allow us to identify genetic, epigenetic or non-genetic abnormalities in HCC and examine a large number of potential markers at once. Nonetheless, there is still a long way to go, since progress is still limited by the sensitivity, specificity and reproducibility of the current technologies, as well as the methods and tools used to analyze the enormous pools of data generated by high-throughput technologies. Integration and optimization of omic-technologies to discover and evaluate potential HCC biomarkers is urgently needed.

Signaling network disorders

Studies on oncogenic events at the molecular and signal transduction network are important to understand the mechanism during hepatocarcinogenesis and accomplish personalized treatment.

HCC represents the best tumor type to study the relationship between tumor and inflammation cells since a majority of HCC arises frequently in inflammatory microenvironment. Up to 80% of HCC cases in China are attributable to hepatitis B virus (HBV) [42]. Hepatitis B virus X protein (HBX), the product of the HBV gene, serves as a multifunctional viral regulator and is implicated in HBV-associated liver carcinogenesis. HBX was reported to be able to induce tumorigenicity of hepatic progenitor cells in 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) treated HBX transgenic mice, by way of activities of IL-6/STAT3 and Wnt/β-catenin signaling pathways [43]. It was elucidated recently that HBX prolonged cell survival during glucose deprivation by regulating redox and energy homeostasis. Under glucose limitation, HBX induced phosphorylation of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylases (ACC) which maintained NADPH and ATP levels via fatty acid oxidation. These data suggest that HBX is critical for HCC cell survival under conditions of metabolic stress and might be exploited for therapeutic benefit [44]. The important oncogene Gankyrin, which is frequently overexpressed in liver cancer, was demonstrated to be upregulated by IL-1b/IRAK-1 inflammatory signaling [45]. IL-1b stimulation causes phosphorylation of IRAK-1, c-Jun N-terminal kinase (JNK), and then recruits the p300/CBP/NF-Y complex to Gankyrin promoter. Inhibition of phospho-JNK impairs IL-1b/IRAK-1 signaling-mediated upregulation of Gankyrin. The finding provides a fresh view on inflammation-enhanced hepatocarcinogenesis and is useful for developing new therapeutic strategies. Damage-associated molecular patterns of high-mobility group box 1 (HMGB1) overexpression has been reported in a variety of human cancers. HMGB1, secreted from hepatocytes in the process of liver inflammation such as NAFLD [46], also has been proven to promote HCC development [47]. HMGB1 activates TLR4-and RAGE-signaling pathways in hypoxic HCC cells to induce caspase-1 activation and facilitate cancer invasion and metastasis [48]. Also, high expression of HMGB1 functions to predict poor prognosis for HCC after curative hepatectomy [49,50].

Tumor initiating cells (T-ICs) represent a minor subset of tumor cells with self-renewal ability, stronger tumor-initiating capacity, and the ability to give rise to more differentiated progeny. Liver T-ICs can be identified using cell-surface markers, such as epithelial cell adhesion molecule (EPCAM) [51], PROM1 (CD133) [52], THY1 (CD90) [53] and OV6 [54]. A recent study presented that the heterogeneous enrichment of miR-429 in liver T-ICs due to abnormal hypomethylated status in promoter region can manipulate hepatocyte self-renewal, malignant proliferation, chemoresistance and tumorigenicity by targeting the RBBP4/E2F1/OCT4 axis. Intriguingly, miR-429 secreted in microvesicles by liver T-ICs could act as a proactive signaling molecule to provide a permissive niche for malignant transformation of surrounding normal hepatocytes. More importantly, secreted miR-429 can be absorbed into circulation and developed as a noninvasive diagnostic biomarker for HCC [55].

Please cite this article in press as: J. Fu, H. Wang, Precision diagnosis and treatment of liver cancer in China, Cancer Letters (2017), https://doi.org/10.1016/j.canlet.2017.10.008