Editorial

Are we getting closer to understanding intratumor heterogeneity in hepatocellular carcinoma?

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Abstract: Hepatocellular carcinoma (HCC) is a highly heterogenous disease and intratumor heterogeneity is a well-known fact within each individual tumor, and may involve morphological, immunohistochemical, and molecular heterogeneities. Understanding of intratumor heterogeneity of HCC should provide critical knowledge about prognosis of the disease and response to therapy. In a recent article by Friemel and colleagues, the investigators utilized a comprehensive approach in linking immunohistochemical markers and molecular changes to morphological intratumor heterogeneity in HCC. The study found that intratumor heterogeneity was detectable in 87% of HCC cases. Combined heterogeneities with respect to morphologic, immunohistochemical, and mutational status of the two most important driver mutations CTNNB1 and TP53 were seen in 22% of HCC cases. The study demonstrates the challenges facing therapeutic strategies targeting single molecules and may explain the limited success so far in developing molecular targeted therapy for HCC.

Keywords: Hepatocellular carcinoma (HCC); intratumor heterogeneity; targeting therapy

Submitted Jan 21, 2016. Accepted for publication Jan 26, 2016.
doi: 10.3978/j.issn.2304-3881.2016.01.06
View this article at: http://dx.doi.org/10.3978/j.issn.2304-3881.2016.01.06

Hepatocellular carcinoma (HCC) is a primary malignant hepatocellular epithelial tumor that frequently occurs in the setting of chronic liver disease and in the background of cirrhosis. The carcinogenesis of HCC is a complex process and is associated with multiple risk factors. HCC may present as a solitary liver nodule or multinodular disease. This may involve one hepatic lobe or scattered throughout the liver. HCC involves multistep carcinogenesis in which dysplastic nodules are precursors to the development of HCC (1,2).

HCC is a highly heterogenous disease and intratumor heterogeneity is a well-known fact within each individual tumor. The pathologic classification of HCC is based on the degree of cellular differentiation. This includes well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated tumors. The cancerous tissue of two different histological grades may be present in a single tumor. Immunohistochemistry may aid in the diagnosis of HCC; staining for pCEA or CD10 is diagnostic of HCC (3,4). The tumor may also stain for other markers such as alpha-fetoprotein (AFP), hepatocyte paraffin 1 (HepPar1), cytoplasmic thyroid transcription factor-1 (TTF1), glutamine synthetase, GPC3, CK8 and CK18. However, not all HCC cells express the tumor marker AFP. Therefore, AFP is insensitive for diagnosis of HCC (5). Immunohistochemical staining showed that p53 and beta-catenin overexpression was significantly related to the histological differentiation of HCC. However, tissue obtained from HCC may exhibit different immunohistochemical characteristics in the same tumor. Furthermore, a wide array of genetic heterogeneity has been described in HCC. It is clear that HCC is less likely to be caused by a single driver mutation.

Intratumor heterogeneity of HCC plays an important role in the prognosis of the disease. The prognosis of HCC is dependent on four important clinical criteria. These

include the severity of underlying liver disease, the size of tumor, lymphovascular invasion and distant metastasis. The intratumor heterogeneity plays a key role in tumor size, cellular differentiation and lymphovascular spread. Well-differentiated small HCC tends to be less aggressive, exhibits a gene expression of hepatocyte function-related genes, and carries a better prognosis while moderately/poorly-differentiated larger tumors tend to have a worse prognosis. These tumors exhibit gene expression through TGF-beta pathway, Akt and Myc pathway (6). Aggressive tumors are characterized by TP53 inactivation mutations, which can be observed in up to 50% of HCC cases. Activation of the pro-oncogenic signaling pathway β-catenin is found in 20–40% of HCC.

Detection of HCC intratumor heterogeneity is important for development of effective targeted therapies. While liver transplantation, surgical resection and radiofrequency ablation (RFA) offer a curative treatment for HCC, it is not an option for patients with intermediate/advanced stage HCC. Sorafenib, a multikinase inhibitor of several tyrosine protein kinases [VEGF receptors and the platelet-derived factor beta (PDGFB) receptor], is implicated in the current treatment of patients with intermediate/advanced HCC. Sorafenib has shown a modest increase in median survival in clinical trial (7). Other anti-VEGFR pathway therapies such as sunitinib, vandetanib, brivanib and bevacizumab have been tested. The vascular heterogeneity within the tumor prevents the acquisition of adequate drug concentration and reduces response to therapy. Furthermore, intratumor heterogeneity plays a role in drug resistance.

Thus, better understanding of intratumor heterogeneity of HCC should provide critical knowledge about prognosis of the disease and response to potential future therapy. By identifying the underlying molecular drivers of heterogenous tumor, specific or combined therapy targeting groups of cells within the tumor may provide therapeutic efficacy.

The recent study by Friemel *et al*. (8), aimed at making a link between morphologic intratumor heterogeneity, immune phenotypes and genetic heterogeneity of the two most important driver mutations in HCC β-catenin 1 (CTNNB1) and tumor protein p53 (TP53) sheds more light on HCC intratumor heterogeneity. A notable strength in this study is the comprehensive approach in linking immunohistochemical markers and molecular changes to morphological intratumor heterogeneity. The study found that intratumor heterogeneity was detectable in 87% of HCC cases. The frequency of morphological intratumor heterogeneity was associated with larger tumor size and higher tumor stage, although it did not reach statistical significance, most likely due to a small sample size. The morphological heterogeneity combined with immunohistochemical heterogeneity was noted in 39% of the cases. Further, combined heterogeneities with respect to morphologic, immunohistochemical, and mutational status of the two most important driver mutations CTNNB1 and TP53 were seen in 22% of HCC cases indicating that these driver mutations are not uniformly present in all tumor regions within the same tumor.

Although the sample size in the study by Friemel and Colleagues was small, the study was powerful in utilizing the combined morphological, immunohistochemical, and molecular approaches to comprehensively document intratumor heterogeneity. The study clearly demonstrates the challenges facing future therapies by targeting single molecules and may explain the limited success so far in developing molecular targeted therapy for HCC. Future studies may improve therapeutic efficacy by identifying the underlying molecular drivers of heterogenous tumors, which in turn may lead to development of specific or combined therapeutic strategies targeting groups of cells within the tumor.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by the Deputy Editor-in-Chief Haitao Zhao (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Friemel J, Rechsteiner M, Frick L, *et al*. Intratumor heterogeneity in hepatocellular carcinoma. Clin Cancer Res 2015;21:1951-61.

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Cite this article as: Hammoud GM, Ibdah JA. Are we getting closer to understanding intratumor heterogeneity in hepatocellular carcinoma? HepatoBiliary Surg Nutr 2016;5(2):188-190. doi: 10.3978/j.issn.2304-3881.2016.01.06

