Correspondence

Understanding intra-tumor heterogeneity and tumor evolution to facilitate hepatocellular carcinoma therapy

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We appreciate this insightful commentary by Zaki *et al.* (1) on our article "Variable Intra-Tumor Genomic Heterogeneity of Multiple Lesions in Patients with Hepatocellular Carcinoma" (2). In this editorial, they highlighted the therapeutic challenge that clinicians face when dealing with advanced hepatocellular carcinoma (HCC), which is the limited therapeutic choices further complicated by intra-tumor heterogeneity (ITH). Such ITH exists in multiple biopsies of a single lesion and multiple lesions in a single liver. Investigating the ITH of HCC can provide important implications on the effectiveness of targeted therapy, i.e., sorafenib (3), and may pave the way for more effective treatment.

Much hope has been attached to "personalized medicine" as the inter-patient tumor heterogeneity is well recognized. The last decade witnessed the success of targeted therapy in several types of cancer, especially the drugs targeting epidermal growth factor receptor (EGFR) in non-small cell lung cancer. Biopsy, which is introduced previously to provide histological evidence for diagnosis, is now also used to unveil the genetic makeup of the patient. Unlike many types of cancer, whose diagnosis is based on biopsy, liver cancer can be reliably diagnosed with radiology alone. However, the use of biopsy may help disease stratification and reveal actionable targets for personalized medicine. Whether biopsy should be applied in the clinical practice of HCC remains a matter of dispute.

Our work reported variable extent of ITH in multiple lesions of the ten HCC patients we investigated. It suggested that, in patients with remarkable ITH, single biopsy might be a biased representation of the tumor. So as Zaki *et al.* pointed out, this further attenuates the value of biopsy in HCC. In patients with less extent of ITH, single biopsy might capture the mutational landscape of the whole tumor. We also found that tumor size was associated with the extent of ITH. A large cohort study of this association is needed to test whether tumor size can be used as a stratification marker of ITH. If it works, single biopsy might capture the genetic makeup of those patients with tumors of small size.

Also as noted by Zaki *et al.*, the phylogenetic trees we built uncovered the nature of branched evolution in HCC, which might explain the failure of drugs targeting a specific signaling pathway. Only the drugs targeting genetic aberrations that locate in the trunk of the phylogenetic tree can stand a chance of reaching clinical benefit. The observation of multiple occurrences in a single patient is an extreme representation of ITH in HCC, which complicates the treatment strategy. Moreover, as demonstrated by the case of combined hepatocellular and cholangiocarcinoma, the ITH of a tumor at the histologic or phenotypic level can be more significant than that at the genomic level, which may further confound treatment decisions and prognosis of these patients.

As Zaki *et al.* suggested, to bypass the barrier set by ITH, "liquid biopsy" seems a promising strategy. Genomic

analyses of circulating tumor cells (4), circulating tumor DNA (5) and other blood-based biomarkers enable non-invasive characterization of the global mutational landscape, monitoring of tumor burden change and detection of drug-resistant mutations. More efforts are needed to improve these methods to finally overcome the hurdle introduced by ITH and facilitate personalized HCC therapy in the future.

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Footnote

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References

1. Zaki MY, Reeves HL. The genetic heterogeneity of hepatocellular carcinoma and the implications for personalised medicine. Transl Cancer Res 2016;5:S1-4.
2. Xue R, Li R, Guo H, et al. Variable Intra-Tumor Genomic Heterogeneity of Multiple Lesions inPatients With Hepatocellular Carcinoma. Gastroenterology 2016;150:998-1008.
3. Llovet JM, Hernandez-Gea V. Hepatocellular carcinoma: reasons for phase III failure and novel perspectives on trial design. Clin Cancer Res 2014;20:2072-9.
4. Ni X, Zhuo M, Su Z, et al. Reproducible copy number variation patterns among single circulating tumor cells of lung cancer patients. Proc Natl Acad Sci U S A 2013;110:21083-8.
5. Dawson SJ, Tsui DW, Murtaza M, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. N Engl J Med 2013;368:1199-209.

