

A bridge between multi-omics data and the management of hepatocellular carcinoma

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Submitted Nov 19, 2014. Accepted for publication Nov 20, 2014.

doi: 10.3978/j.issn.2305-5839.2014.12.01

View this article at: <http://dx.doi.org/10.3978/j.issn.2305-5839.2014.12.01>

Recent technological advancements in comprehensive genome and transcriptome analyses have clarified the molecular pathways underlying the development of human hepatocellular carcinomas (HCCs). However, there is still a gap between the results of multi-omics analyses and their clinical implications. Because of the large quantity of data obtained through these types of analyses, identifying target molecules important for clinical uses is difficult.

Miao *et al.* linked multi-omics results with the management of HCC (1). They performed whole genome sequencing of noncancerous liver samples and multiple HCC nodules of the same patients. They distinguished two types of nodules—metastatic nodules derived from a primary tumor and multicentric nodules that occur synchronously—and successfully clarified the clonality and aggressiveness of multifocal HCCs. For example, metastatic nodules showed a sequential progression of genetic alterations from the primary tumor to the portal vein thrombus and metastatic satellite metastatic lesions. Previously, Tao *et al.* also analyzed mutations in multiple nodules of the same patients using whole genome data; they elucidated cancer growth dynamics and the associated mutations (2). It is possible that comprehensive analyses of genetic alterations should be a powerful tool to distinguish metastatic lesions from the multicentric occurrence of HCCs, and to manage HCCs. For example, the recent development of direct-acting antiviral agents for hepatitis C has enabled the eradication of the virus even in patients with advanced liver cirrhosis and HCC (3). It is also known that a sustained virologic response after treatment of hepatitis can decrease the emergence of HCC and mortality. Therefore, if it could be demonstrated that nodules were not metastatic but instead originated from independent

tumors, such patients would be suitable for antiviral therapies after the curative treatment of HCC, preventing recurrence. Moreover, the indication of liver transplantation for patients with HCC could be expanded by this type of molecular analysis. Typically, the Milan criteria are applied for selecting cases with HCC that are appropriate for liver transplantation. However, it is possible that the risk of recurrence differs for patients with and without metastatic lesions. From this point of view, the clonality of multifocal nodules should be considered for the indication of liver transplantation in HCC patients.

Using a large patient cohort, Miao *et al.* also identified the key mitotic checkpoint regulator *TTK* as a promising overall prognostic marker for HCC (1). Based on the transcriptome analysis, more molecules responsible for cellular function were found to be deregulated to a greater extent in metastatic lesions than in primary tumors. On the other hand, gene expression alterations in non-metastatic nodules resulting from multicentric occurrences were trivial. *TTK* expression was significantly correlated with tumor grade in the expression analysis using a large cohort of HBV-positive HCC cases. Importantly, *TTK* mRNA expression levels were inversely correlated with the recurrence-free survival and overall survival of these patients. The group with high *TTK* expression showed shorter times to HCC recurrence than the group with low *TTK* expression. This finding could also have clinical importance because it affects the HCC management strategy; the selection of HCC cases for invasive treatment including liver transplantation, and the need for antiviral treatment for HCV-positive cases after curative treatment of HCC (4). Further validation using HCV-related and non-viral HCC patients is necessary because the mutational profile might differ between HBV-

positive and -negative HCCs (5,6). Nevertheless, it is possible that “omics” analyses will be a powerful tool for the development of a cure for liver disease including HCC in the near future.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Nishida N, Kudo M. A bridge between multi-omics data and the management of hepatocellular carcinoma. *Ann Transl Med* 2015;3(1):1. doi: 10.3978/j.issn.2305-5839.2014.12.01