

New 'multi-omics' approach and its contribution to hepatocellular carcinoma in China

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Hepatocellular carcinoma (HCC) is one of the most common liver neoplasms worldwide, and 70-80% cases are accounted in Asian countries (1). Etiological background of HCC patients is different in each country or area. In China, infection of hepatitis B virus (HBV) is a main etiological factor of increased incidence of HCC. In fact, 93 million HBV carriers are Chinese, accounting for 2/3 of such patients worldwide, and about 20 million of these people have chronic HBV infection (2). Chronic HBV infection is a high risk factor for development of HCC. Therefore, the follow-up of those chronic viral hepatitis type B patients and the early-detection of HCC in those patients are pressing tasks to reduce the incidence of HCC in China (3).

Recent years, various omics analyses have rapidly advanced with the development of next generation sequencing technology. Those omics analyses including genomic, transcriptomic and proteomic analyses can provide the huge amount of data regarding genetic alteration and gene or protein expression level. The combination of those omics analyses can overview the perturbed systems in the cell or tissue. Furthermore, the advanced technologies of bioinformatics enable construction of reliable and significant dataset. The combination of omics analyses and bioinformatics can contribute to the personalized medicine and the discovery of new diagnostic or therapeutic target, but the difficulty still remains in integration of those dataset, delineation of physiological pathway that affect significantly in disordered specimen (4,5).

The study of multi-omics analysis performed by Miao *et al.*, entitled "Identification of prognostic biomarkers in hepatitis B virus-related hepatocellular carcinoma and stratification by integrative multi-omics analysis" can provide the foundation of genetic and transcriptomic analyses against individual patients'

HCC tissues (6). Whole-genome sequencing analysis of HBV-related HCC patients revealed the different HBV integration pattern and mutations in coding sequence, suggesting the different tumor clonality in the primary-metastatic tumor tissues or the synchronous tumor tissues. This analysis can be used for the evaluation of HCC characteristics from the genomic similarities of all tumors in the individual patient and contribute to the decision-making of treatment strategy. They also perform the transcriptomic analysis and revealed that genes related to cytoskeleton organization and extracellular matrix organization were up-regulated in patient who had cirrhosis and multifocal, poorly differentiated HCC (died of recurrence) but not in patient who had non-cirrhosis and multifocal, well differentiated HCC (no recurrence). In addition, 21 genes related to cell cycle, p53 signaling pathway and histidine metabolism were found to be enriched in HCC of patient who had bad prognosis. Comparative analysis of gene expression level to clinicopathological characteristics in 174 HBV-related HCC patients showed expression level of *SFN*, *TTK*, *BUB1* and *MCM4* were significantly related to Edmondson tumor grade. Although further validation study is necessary, these results suggested that multi-omics approach can contribute to the characterization of individual HCC and the discovery of clinicopathologically significant genes.

Altered expression of those identified genes had partly studied and suggested the relationship with the role of carcinogenesis and cancer progression in HCC or other cancers (7-9). In the study of drug resistance using HCC cell lines, increased TTK expression induced the sorafenib-resistance as well as up-regulation of cell proliferation in HCC cells (8). In addition, TTK overexpression was detected in 86.8% (46/53) of HCC tissue specimens. This

rate coincides with the rate of high *TTK* gene expression in the result of transcriptomic analysis performed by Miao *et al.* (6). To perform further biological study to clarify the functional role of *TTK* in HCC, *TTK* can be developed as a diagnostic marker and a therapeutic target.

Serological detection of tumor marker is easy and effective as a diagnostic and follow-up method of HCC. Currently, simultaneous evaluation of two tumor markers [e.g., alpha-fetoprotein (AFP) and des-gamma-carboxyprothrombin (DCP)] is recommended in J-HCC guideline (10,11). In contrast, only AFP has been recommended and widely used for the diagnosis of HCC in China. Our research group demonstrated a multi-center case-controlled study in China to investigate the clinical utility of simultaneous evaluation of AFP and DCP (12). As results, we found that simultaneous measurement of AFP and DCP could achieve a better sensitivity in diagnosing Chinese HCC patients, even for small tumors. We consider improvement of the diagnostic ability of serum biomarkers for HCC contributes to reduce the current high incidence of HCC patients in China.

Systematic medical care for HCC is being advanced in China. Introduction of effective tools (e.g., tumor marker) and the standardization of medical care (e.g., construction of guideline) are considered to be important for improving HCC patients' prognosis (13). Novel factors discovered by multi-omics analysis of HBV-related HCC specimens are expected to develop new effective method of diagnosis and therapeutics for HCC.

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