

Wading through the noise of “multi-omics” to identify prognostic biomarkers in hepatocellular carcinoma

Karen Pineda-Solis, Vivian McAlister

Department of Surgery, University of Western Ontario, London, ON, Canada

Correspondence to: Vivian McAlister, Co-editor of the Canadian Journal of Surgery. Department of Surgery, University of Western Ontario, 339 Windermere Road, London, ON, Canada. Email: vmcalist@uwo.ca.

Abstract: Multi-omics, the molecular analysis of genes, transcriptional RNA and proteins, allows researchers document the mechanism of action of a target gene. However multi-omics may result in an avalanche of information when used to screen a population. It is very difficult to discern a pattern or signal related to a disease or its progression. Differential multi-omics exploits our ability to see differences between subjects who are similar in all respects except for the outcome being tested. Twin studies are an example of this. Miao and colleagues compared two patients who had diverse outcomes following treatment of multifocal hepatocellular carcinoma (HCC) to identify seven candidates as the responsible genes. In a larger cohort of patients with HCC they narrowed the field down to a single target down. By looking at progression of HCC, they isolated TTK, a protein kinase which disrupts the interaction of the tumour suppressor p53 with the oncogene *MDM2*. *TTK*-high tumours recurred 3 times faster than *TTK*-low tumours.

Keywords: Hepatitis C virus (HCV); hepatitis B virus (HBV); hepatocellular carcinoma (HCC); genomics; multi-omics

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A little over a decade ago, we reviewed the potential for new techniques in the basic science of genetics to influence clinical care (1). We found the task faced by scientists to be daunting and the prospect of success seemed distant. Since then techniques advanced from gene mapping to include transcription, protein and other characteristics of cell function encompassed in the neologism “multi-omics”. Information available is increasing exponentially. If it was hard to pick a signal out of the noise 10 years ago, it is many times harder now. Using a deceptively simple experimental design, Miao and colleagues at the Peking Union Medical College, have cracked the nut (2).

By comparing two patients with hepatitis B virus (HBV) and multifocal hepatocellular carcinoma (HCC), they pulled out seven candidate genes that may be related to the capability of the tumour to metastasize. Examining the candidates in a cohort of patients with HCC associated with hepatitis C virus (HCV). They reduced the group to six. By looking at progression of HCC, they isolated *TTK*, a

protein kinase which disrupts the interaction of the tumour suppressor p53 with the oncogene *MDM2*. *TTK*-high tumours recurred 3 times faster than *TTK*-low tumours.

A variety of risk factors have been associated with HCC (3). The prognosis after the proper treatment in HCC (either surgical or local treatment) depends on intrinsic factors of the tumour (4). The current guidelines for the diagnosis of HCC recommend liver biopsy for hepatic nodules with atypical features of imaging (5). For HCC, there has been increasing demand for classifications to predict the biological behaviour and prognosis of the cancer. Most of these classifications are morphological (6).

It has long been the goal of research to refine histology by examining cellular pathways, particularly those related to the cell cycle. In order to separate cancers with high malignant potential from those less likely to metastasize or recur.

In 2004, Lee and colleagues used gene sequencing to identify two gene predictors of a likelihood of HCC recurrence and suggested that JAK/STAT and NOTCH1

pathway inhibitors may have a role in preventing this outcome (7). On the other hand in 2007, Boyault and colleagues found a diverse array of signals when they performed global transcriptome analyses on 57 HCC and attempted validation in another cohort of 63 patients (8). This has not stopped others from developing strategies for “genomics-driven oncology” (9,10).

Miao and colleagues need to test their hypothesis in a second cohort of patients with HCC in order to determine the magnitude of its effect. The mechanism is probably shared with other cancers that may be tested as well. Fruitful areas of investigation will be to understand the effect on clinically used tyrosine kinase inhibitors of TTK function. Specific TTK inhibition is a therapeutic option but its effect on hepatocyte function will have to be understood. The excellent paper by the Peking Union Medical College team, which reads like an exciting detective story, may well lead to a happy ending, progress in treating a difficult cancer that affects millions of patients worldwide.

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Footnote

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