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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

The Quest for Relevant Hepatocellular Carcinoma Biomarkers

Interest in the field of -omics within the past decade has led to further advancement in the understanding of numerous biochemical pathways as well as their dysregulation in pathology. The technologies allow characterization and quantification at various molecular levels (genes, transcription factors, proteins, and metabolites), enabling the study of key genetic and epigenetic pathways. Importantly, by phenotyping organisms at various molecular levels, -omics applications can be translated into molecular diagnostics and therapeutics in a clinical setting.

Such technology has been of particular importance for hepatocellular carcinoma (HCC), which has an abysmal mortality rate, primarily because of its late presentation.[1] If, by surveillance or chance, a tumor is detected at an early stage, curative interventions, such as hepatic resection and orthotopic liver transplant, are feasible and offer excellent prognostic results.[2] α-Fetoprotein, as the historical biomarker, has been made largely redundant as a result of poor sensitivity and specificity.

The lack of an alternative biomarker creates a pressing need to apply such -omics technologies to identify reliable and robust metabolic signatures.[3] By using Warburg's[4] original hypothesis from 1924, new metabolomics enquiry has focused on this theory of altered metabolism—the preferential utility of glycolysis instead of oxidative phosphorylation in tumorigenesis, maximizing proliferative cellular constituent products at the expense of efficient energy production. Thus, several metabolic profiles now have been identified in the context of HCC. Some early Chinese studies and the recent European Prospective Investigation into Cancer and Nutrition study in Europe have identified the significance of free fatty acids, ketone bodies, and lipoproteins, reinforcing the anaerobic nature of tumorigenesis by β-oxidation in heterogeneous population groups.[5,6] For example, reductions in several lysophosphatidylcholines, such as lysophosphatidylcholines C16:0 and C18:0, compounds involved in endothelial cell migration,[7] have been indicated in HCC tissue metabonomics. In addition, there have been fascinating results highlighting the diversity of HCC and showing changes in certain saturated lipids were associated with specific transcriptomic classification of tissues.[8] Furthermore, the combination of betaine and propionylcarnitine levels in tissues and serum showed promising diagnostic potential to distinguish HCC from chronic hepatitis and cirrhosis.[9]

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Nwosu et al[10] have compiled an extensive database of genes implicated in human HCC from the analysis of HCC tissues, validating previous findings and identifying novel targets. By testing a broad network of genes implicated, their results have an important role in bringing together previously identified markers within this field. The findings reinforce widely agreed on hypotheses, such as the down-regulation of genes involved in gluconeogenesis, urea cycle, fatty acid metabolism and xenobiotic metabolism. By correlating their results with tumor progression, size, and overall survival, they have added valuable information surrounding the predictive merit of genetic expression, such as the reduced expression of both aldolase, fructose-bisphosphate B gene and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1 gene, showing correlation with survival. In the analysis, Nwosu et al[10] also highlighted the potential importance of impairment in the fatty acid metabolism pathway in early HCC diagnosis. Dysregulation of fatty acid metabolism and genes implicated in the serine pathway (Phosphoglycerate dehydrogenase gene, Phosphoserine aminotransferase 1 gene, serine hydroxymethyltransferase 1 gene, serine hydroxymethyltransferase 2, glycine dehydrogenase gene) have been highlighted in the development of nonalcoholic fatty liver disease, but descriptions have been limited within the general pathogenesis of HCC.[11] In addition to this, previously unrecorded nucleotide biosynthesis targets have been identified, namely thymidylate synthase gene, cytidine deaminase gene, and dihydropyrimidine dehydrogenase gene. The investigators noted that these genes have been implicated previously in the development of colorectal cancer via glycan metabolism.[12] If these novel pathways have a significant role in HCC pathogenesis, it will be fascinating to observe the therapeutic role of the identified genes in the future.

Within the -omics platforms, it is crucially important to actively prioritize translational prospects of the findings. Several studies have expanded the search beyond tissues and serum into more readily available clinical material, such as saliva and urine. In consideration of the targeted burden of HCC in resource-limited settings of sub-Saharan Africa and South East Asia, a simple diagnostic test, such as a urinalysis to identify evidence of tumorigenesis, would be a significant step in addressing the burden of malignancy.[13] To this end, Nwosu et al[10] have provided novel insight within the search for HCC biomarkers by using advanced -omics technology. This is an encouraging new step for the diagnosis and treatment of HCC, not only for those resource-limited areas with a high disease burden, but also for identifying individualized interventions in the context of personalized medicine.

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Conflicts of interest
The authors disclose no conflicts.

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