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Editorial

Ariadne's Thread in the Network of Hepatocellular Carcinoma Immunobiology

John Koskinas* and Athanasios Armakolas

2nd Academic Department of Medicine, National and Kapodistrian University of Athens, Medical School Hippokration General Hospital, Athens, Greece

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Hepatocellular carcinoma (HCC) accounts for approximately 90% of primary liver cancers and represents a major global health problem. The main risk factors responsible for the development of HCC are chronic viral infections, non-alcoholic fatty liver disease, and alcohol-related liver disease, with wide geographical distribution.[1] HCC development and growth involve multiple factors and pathways that lead to changes in gene expression, immune interactions and changes in the tumor microenvironment. In recent years, much progress has been made in understanding the mechanisms underlying tumor-immune system interactions and immunotherapy has been successfully applied to many tumors. Moreover, cancer-specific immune prognostic signatures have been evaluated in order to predict prognosis and response.[2]

Immune reconstitution and restoration of immune cell function against the tumor is the optimal target of immunotherapy. The factors that play a critical role are complex. HCC is a very heterogeneous tumor, with low/moderate mutation burden and microsatellite instability affecting antigenicity.[1,3] Etiology of the underlying liver disease, i.e. chronic hepatitis C virus/hepatitis B virus (HCV/HBV) infection vs. non-alcoholic fatty liver, may also have an impact on the immune system function and the constitution of liver microenvironment, resulting in immune tolerance and development of HCC.[3]

Current immunotherapy for advanced HCC is based on the utility of immune checkpoint inhibitors, namely programmed cell death 1 receptor (PD-1), programmed cell death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), administered as monotherapy or combination therapy and having an up to 35% objective response rate.[4] However, response to treatment is not related to PD-L1 expression, suggesting that more complex mechanisms are involved in immune intervention. In fact, tumor heterogeneity, new tumor antigen formation and alterations in the immune response and microenvironment make selection of patients and type of immunotherapy a very hard task. Furthermore, immune markers for identification of immunologically "hot" HCC and evaluation of treatment response in clinical practice are lacking.

In the past decade there has been an explosion of healthcare-related data with digitalization of medical records and utilization of new sophisticated molecular testing for analysis of various genetic, cellular and tissue biological parameters ("omics").

Big data, by nature, are infinitely versatile and powerful. Extensive analysis and combination of various datasets give a great ability to create powerful algorithms for robust immune-related gene signatures and open a new avenue towards personalized therapy in HCC.

Targeted immunotherapy is actively investigated, with the aim of inhibiting aberrant oncogenic pathways and remodeling the immune microenvironment so as to improve prognosis.

In this issue, Hong *et al*.[5] gives a bird's-eye view of the incredible depth and scale of big data prior to the determination of possible targets for immunotherapy in HCC microenvironment.

The authors systematically integrated genomic profiling to illustrate a global portrait of the HCC immune microenvironment, in order to identify immune-related genetic changes. Key immune-relevant genes (KIRGs) were obtained through integration of the differentially-expressed genes of The Cancer Genome Atlas (TCGA), immune genes from the Immunology Database and Analysis Portal (www.ImmPort.org), and immune differentially-expressed genes determined by single-sample gene set enrichment analysis (ssGSEA) scores.

They found that among the 21 KIRGs involved in the pathogenesis and progression of HCC, four genes (IKBKE, IL2RG, EDNRA, IGHA1) seem to be equally or more important to PD-L1. This theory was verified through analysis of tissue expression in HCC samples. The fact that the most significant immune-related molecules obtained by this analysis are major effectors of many oncogenic pathways, promoting transformation in many cancers, renders them possible candidates for HCC treatment. To further investigate the possible regulation mechanism and identify a regulatory network for the involved genes, they studied their relative transcription factors and the long non-coding (lnc) RNAs. They found that the IKBKE gene was mainly related to lncRNA AC127024.5, with NRF1 being its most relevant transcription factor. This axis was found to be involved in

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ISG, interferon-stimulated gene; KIRG, key immune-relevant gene; lncRNA, long non-coding RNA; PD-1, programmed cell death 1 receptor; PD-L1, programmed cell death-ligand 1; ssGSEA, single-sample gene set enrichment analysis; TCGA, The Cancer Genome Atlas.

***Correspondence to:** John Koskinas, 2nd Academic Department of Medicine, National and Kapodistrian University of Athens, Medical School Hippokration General Hospital, Athens, Greece. E-mail: koskinasj@yahoo.gr

many biological pathways of HCC and could therefore be a potential therapeutic target.

In previous studies, IKBKE has been found to be overexpressed in various kinds of tumors, including HCC. Apart from its tumorigenic function, exerted through various signaling pathways, it also regulates the secretion of inflammatory cytokines and thus affects the tumor microenvironment.[6]

Finally in the current study, a risk score model, based on the KIRGs-lncRNA network, was created and evaluated in the testing cohort of patients. It showed good correlation with immune check point genes and infiltration of the microenvironment with CD4, macrophages and neutrophils.

Data from other studies have shown aberrant biogenesis of distinct lncRNAs in HCC. Their role is still elusive, but by binding with DNA, RNA or proteins they modulate oncogenesis and the tumor microenvironment.[7] Furthermore, recent evidence suggests that HCV upregulates the level of a series of lncRNAs that inhibit the expression of IFN-stimulated genes (ISGs), leading to immune suppression and chronic inflammation, both of which are associated with the development and progression of HCC.[8]

Moreover, studies that have explored and analyzed immune multi-omics databases have shown: 1) a significant overexpression of checkpoint genes (PDCD1, CD274, PDCD1LG2, CTLA4, CD86, CD80) in a subtype of HCC characterized by increased immune cell infiltration score (including tumor matrix, immunity, purity);[9] and, 2) a molecular signature based on 10 immune genes with prognostic role.[10]

In line with the aforementioned findings, the evidence analyzed in the study being discussed herein unveils new associations between tumor and immune interface and provides new insights into the mechanisms of the disease and possible treatment. Furthermore, these results provide additional information that can be incorporated along with other algorithms obtained by bioinformatics into the selection and management of patients with advanced HCC.

Although identification of immune genes renders a very useful set of targets for the development of novel targeted therapies, the steps towards clinical practice must be taken with great caution. The exploration journey towards new immunotherapy agents needs to be fully traveled. Along this route, it will be important to identify and prioritize patients who could benefit from such therapies.

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