The complexity of immune cell landscape in hepatocellular carcinomas with different risks—reply letter

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Response to: Ocker M. Dissecting the immune cell landscape in hepatocellular carcinoma—are we understanding complexity? Ann Transl Med 2020;8:666.

Thank you for the invitation to respond to the editorials by Matthias Ocker on our recently published paper "Clinical significances of immune cell landscape in hepatocellular carcinoma (HCC) patients with different degrees of fibrosis". Our studies revealed that the fraction of resting mast cells and activated natural killer (NK) cells were significantly different between HCC patients with different fibrosis degree. Meanwhile, the genes participating those immune function and correlated with patients' overall survival and relapse-free survival were identified. The results suggested that PVRIG involved in T cell CD8^{+} infiltration and NK cells is significantly positive associated with well-known checkpoint molecules (1).

In our studies, 212 HCC samples with fibrosis Ishak score from TCGA dataset were used. According to the editorials, we investigated the TNM stage, specimen collection method and virus infection of these samples. The numbers of HCC samples in stage I, stage II and stage III/IV are 108 (50.94%), 51 (24.06%) and 42 (19.81%), respectively. Most of HCC samples were in the early disease stages and 202 (95.28%) samples underwent curative surgery. Meanwhile, 90 (42.45%) samples were infected with viral hepatitis and the TCGA clinical information were not described whether the samples were with non-alcoholic fatty liver disease (NAFLD). Due to the sample sizes and bias in different TNM stages, our results may not be entirely representative for real HCC samples.

Furthermore, we have tried to find an independent dataset to validate our results in the database GEO (https://www.ncbi.nlm.nih.gov/geo/) and ArrayExpress (https://www.ebi.ac.uk/arrayexpress/). Unfortunately, the expression profile with information of fibrosis degree and outcomes was not found. To investing the immune cell landscape in HCC with various fibrosis degrees and the underlying etiologies, there are lots of works to do in future.

Immune checkpoint blockade (ICB) has been reported to reactivate the antitumor immune response through blocking the inhibitory immune system (2). Immune checkpoint inhibitors are expressed primarily by T cells (for example, CTLA4, PD-1, HAVCR2 and LAG3) or by the tumor and other immune cells (for example, PD-L1). Right now, some inhibitors of CTLA4, PD-L1 and PD-1 have been used in kinds of solid cancers, including HCC (3). Two clinical trials in HCC, named CheckMate040 and Keynote224, has been reported by using nivolumab and pembrolizumab respectively (4,5). Both of these trials suggested more clinical benefit compared to sorafenib treatment in advanced HCC. Right now, the response rate for single-agent ICB is approximate 15–20% in the treatment of HCC. What's more, 15–25% of these ICB-treated patients has experienced 3/4 treatment or immune-related adverse events (3). So, deeply understanding of molecular mechanism of immunotherapy and predictive biomarkers of response is a difficult challenge for improved

clinical benefit to the HCC patients.

Previous studies have been revealed that tumor-infiltrating lymphocytes (TILs), including CD8+ T cells, are resulted in better prognosis of HCC (6). Recently, B cells and tertiary lymphoid structures associated with survival and immunotherapy response in sarcoma (7). Melanoma (8) and renal cell carcinoma (9) were also been reported. Our studies tried to reveal the differences of immune cell fractions in HCC patients with different fibrosis degrees and to select possible targets for improving immunotherapy. Our results suggested that, PRIVG, as a novel biomarker, is significantly associated with survival which is expressed on T cells and inhibiting T cell receptor-mediated signals. The results of Person correlation coefficient found that PVRIG is significantly positive related (R: 0.35–0.67) with other checkpoint molecules, such as *PDCD1*, *CTLA4* and *Teff* gene signatures. With the novel expression profiles and novel methods to quantify and analysis the immune landscape of HCC, more and more biomarkers could be identified. The response rate of immunotherapy could be raised and clinical outcomes could be better in feature.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-2020-92). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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