Editorial

Dissecting the immune cell landscape in hepatocellular carcinoma—are we understanding complexity?

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Despite its high global prevalence and increasing incidence, treatment of advanced hepatocellular carcinoma (HCC) remains unsatisfying. Since the introduction of the first multi-kinase inhibitor sorafenib more than 10 years ago, only incremental benefit has been achieved in first and second line settings resulting in a dismal five-year survival rate of only 1% (1). In addition to a high intrinsic resistance of HCC cells to cytotoxic agents, no clear oncogenic driver has been identified so far which could be used for targeted therapies (2). A reason for this could be the fact that HCC usually develops as a "disease within a disease", i.e., based on underlying chronic viral infections, chronic inflammatory conditions like NASH and the association with different degrees of fibrosis and cirrhosis. This pathophysiologic heterogeneity is commonly neglected when trying to identify novel predictive biomarkers for HCC (3), leading to only small and less comparable subpopulations.

Cancer immunotherapy (CIT) has evolved as a novel means to overcome these limitations. The development of immune checkpoint inhibitors like the anti-CTLA4 antibody ipilimumab or anti-PD1/PD-L1 antibodies like pembrolizumab, nivolumab or atezolizumab has dramatically changed the treatment landscape in various solid tumors and achieved long-lasting clinical responses in, e.g., melanoma or non-small cell lung cancer (NCSCLC) (4). Several CIT approaches have been studied in HCC but the achieved response rates of about 15–20% are considered only modest (5,6). Considerable efforts are therefore taken to identify better predictive biomarkers beyond expression of PD-1/PD-L1 or tumor mutational burden. The commonly found chronic inflammatory conditions underlying HCC strongly impact on the immune cell activity needed for successful CIT and esp. cirrhosis has been associated with severe immune dysfunction. In a recent publication, Tang *et al*. therefore investigated the composition of the immune cell landscape in HCC in relation to its underlying fibrosis or cirrhosis to better understand which patients would benefit from established or novel CIT approaches (7).

The authors used two independent gene expression profiles (GEO, TCGA) and performed a bioinformatics analysis (CIBERSORT) to quantify relative levels immune cell types within the gene expression data sets. Results were then further correlated with survival analysis and clinical parameters. Significant differences were found between different stages of cirrhosis, dysplasia and HCC for T cell subpopulations, plasma cells and innate immune cells. In brief, the results show that multiple components are dysregulated during HCC formation and that both T cell immunity as well as myeloid cells are affected to create an immunosuppressive environment. In a second step, differentially expressed genes related to immune cell function were identified and correlated to overall survival (OS) and recurrence free survival (RFS) in the HCC

subpopulation. Here, PVRIG (PVR related immunoglobulin domain-containing, CD122R) and FCER1A (Fc fragment of IgE receptor Ia) were found to be significantly associated with OS and RFS. Both genes are known to be associated to immune checkpoint inhibitors like CTLA4 or LAG3 or to NK or mast cell function (7-11). The study confirms previous results from Rohr-Udilova *et al*. but nicely expands the data by including fibrosis scores into the analyses (12).

These findings are of importance as they demonstrate that algorithms based on gene expression profiles (CIBERSORT) can identify immune phenotype subsets that may lead to the identification of potential novel predictive or prognostic biomarkers. While current CIT focuses largely on (reactivation of) T cell populations, the findings from Tang *et al*. indicate that also non-T cells might play an important tole in creating an immune evasive environment. In a recent publication, the role of PD-1 in contributing to anti-tumor immunity was demonstrated also in myeloid cells in mice (13). Interestingly, this phenotype was associated with metabolic alterations in glycolysis and with hypercholesterolemia, indicating also a potential new link to NASH and HCC formation by myeloid cells depleted of PD-1. Yet, such data also imply that myeloid cells should be taken into consideration as a potential predictive biomarker also for current CIT. While direct evidence in HCC is still missing, both intratumoral and extratumoral macrophages and myeloid derived suppressor cells were correlated to poor response to immune checkpoint blockades in other tumors (5). Including such cell types in predictive biomarker panels may thus improve the so far mediocre response rates of CIT in HCC, too.

Some aspects also need critical attention. So far, only the retrospective database derived data is available which provides a good overall basis and allows hypothesis generation but may not be entirely representative for real life patient samples and data. Due to the early disease stages recruited into TCGA studies (patients often underwent curative surgery), only a small number of the approx. two hundred HCC cases available has metastatic or advanced disease stages. Interestingly, NAFLD was diagnosed only in less than 10% of cases while viral hepatitis (alone or in conjunction with other risk factors) was seen in about one third of cases. This underlines the importance to validate the obtained data in an independent and prospective study that needs to be adequately powered for small subgroup analyses and to account for the various underlying etiologies and the differential status of inflammation.

In summary, such studies create important unbiased data that identify potential new biomarkers that are of importance to improving the outcome of patients with HCC, but may need additional clinical validation and real life data from clinical trials.

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Footnote

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