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Commentary

A novel immunosuppression-based classification of liver tumors opens new perspectives for adapted therapeutic strategies

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Liver cancer, including hepatocellular carcinoma (HCC), is the 4th leading cause of cancer-related death worldwide, notably as a result of tumor heterogeneity which hampers the development of efficient treatments. Integrative genomics helped with characterizing heterogeneity in cancer, leading to molecular stratification of tumors and adapted therapeutic strategies for specific tumor subtypes.

In this article of *EBioMedicine*, Fujita and colleagues report the results of an elegant meta-analysis of RNA and whole genome sequencing data from 234 liver primary tumors [1]. Based on immune signatures and genomic alterations, four tumor subtypes are highlighted. Three subtypes exhibit mutually exclusive immunosuppressive features associated with infiltration of regulatory T cells or tumor-associated macrophages (TAM) and *CTNNB1* mutations. One subtype associated with a better prognosis shows cytolytic activity. The study brings important information on the immunosuppressive properties of HCC microenvironment. Notably, the non-inflamed TAM subtype is enriched in *ARID2* mutations resulting in impairment of chemokine production and a weaker inflammatory and interferon-γ response. By taking into account immunosuppressive mechanisms, the study improves the current binary immune classification into "inflamed" or "non-inflamed" tumors. From a clinical perspective, understanding HCC immunosuppressive properties is critical to improve the efficacy of immune-based therapeutic strategies.

Over the last decade, immune checkpoint inhibitors and CAR-T cells emerged as innovative therapeutic options. Both have shown promising results in several cancers but not in liver cancer, particularly as a result of frequent intrinsic tumor immunosuppression [2,3]. Notably, CAR-T cell therapy is hampered in HCC by the limited migration of T cell into the tumor, the immunosuppressive tumor microenvironment and the lack of well-defined tumor antigens [4]. Concerning immune checkpoint inhibitors, the phase III randomized controlled trials comparing nivolumab versus sorafenib in first line or pembrolizumab versus placebo did not reach their pre-specified endpoints. The lack of efficacy for these two PD-1 inhibitors suggests that a better stratification of HCC patients based on the immune microenvironment is required to identify the patients who may benefit from immune-based therapies [5]. By improving the current immune classification of HCC, the study of Fujita et al. may help to identify the patients who most likely could respond to immunotherapy. Importantly, this proposed immunological classification is validated in Asian and Western datasets and therefore could be applied to a large cohort of patients independently from HCC etiology.

Immunotherapy in HCC not only lacks relevant biomarkers to identify the best responder patients, but also a deep characterization of molecular mechanisms generating an immunosuppressive microenvironment. Fujita et al. identifies tumor-specific immunosuppressive mechanisms which could be targeted to improve efficacy of treatments, including innovative strategies combining immune-modulatory agents and anti-tumor compounds. Several studies have already demonstrated the potential benefit of such combined therapies. Thus, co-treatments with PD-1 inhibitors and kinase inhibitors (e.g. lenvatinib, sunitinib) improve anti-tumor responses and tumor regression. Combination of PD-1 and CTLA-4 inhibitors that have shown great results in melanoma are also currently tested in HCC. Similarly, the efficacy of PD-L1 inhibitors (e.g. avelumab) are being evaluated with sorafenib or axitinib in patients with advanced HCC. Sorafenib, a multi-kinase inhibitor, exhibits immunomodulatory although the underlying molecular mechanisms are unclear [6]. In immunodeficient mice, sorafenib enhances the efficacy of human CAR-T cells against HCC [7]. These results suggest that combining immunotherapy and drugs presenting immunomodulatory effects represents a promising effective therapeutic strategy in HCC. Thus, efficient immunotherapy in HCC will need both a clear comprehension of immunosuppressive mechanisms and the development of effective drug combination. In this context, molecules or pathways involved in immunosuppression and cancer progression represent ideal targets. Transforming Growth Factor beta (TGFβ) is such a relevant target, inducing tumor microenvironment remodeling and exhibiting potent immunosuppressive features. Interestingly, Fujita et al. report enrichment of a TGFβ signature in the TAM HCC subtype, in agreement with our recent study demonstrating that TGFβ and AXL induce CXCL5 and neutrophil recruitment in poor prognosis HCC [8]. Accordingly, galunisertib (LY2157299), an inhibitor of TGFβ

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pathway, is currently being investigated in several clinical trials. Combined therapeutic strategies associating galunisertib with PD-1/PD-L1 inhibitors, or bifunctional trap fusion proteins targeting both TGFβ and PD-L1, such as the M7824 compound, are also attractive [9]. Supporting this strategy, it was recently reported that TGFβ attenuates the efficacy of immune checkpoint inhibitors by modulating the tumor microenvironment and restricting T cell infiltration [10].

In conclusion, the study by Fujita and colleagues contributes to improve our knowledge on immunosuppressive features of specific HCC subtypes and opens new avenues for the development of effective targeted immunotherapy.

Declaration of Competing Interest

All authors have no conflicts of interest to disclose.

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