RESPONSE TO CHECKPOINT BLOCKADE IN HCC IS ASSOCIATED WITH IGG1 SKEWING

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Background Immune checkpoint blockade (ICB) is increasingly becoming the standard of care for many tumor types. Yet, useful predictive biomarkers for benefit from ICB are still lacking. Emerging literature has suggested the importance of intra-tumoral B cells in response to ICB; however, these studies fail to address the heterogeneity amongst B cells responses.1-4 Here, we describe the largest single-cell RNA sequencing (scRNAseq) data set of B cells in treatment-naive and ICB-treated hepatocellular carcinoma (HCC) patients and find specific B cell phenotypes that are highly associated with response to ICB.

Methods A cohort of 44 patients with early-stage HCC underwent surgical resection, of which, 26 patients received neoadjuvant anti-PD-1 treatment. Pre-and post-treatment blood and representative samples from resected tumor and adjacent uninvolved liver were collected fresh, and 10x scRNAseq was performed on the immune cell compartment. ELISA was performed on plasma from each patient to detect antibodies against a panel of 26 tumor antigens.

Results We identified three major subsets of B cells: naïve, memory (Bmems), and plasma cells (PCs), and identified different clusters within each subset with distinct transcriptional signatures. Bmem and PC clusters demonstrated differential expression of the immunoglobulin isotypes and subclasses, and we hypothesized that the B cell response in ICB responders might be skewed towards an IgG1 phenotype. Indeed, we observed that non-responders had a higher proportion of Bmems from clusters with the lowest IgG1 expression, while responders had an enrichment in Bmems originating from the cluster with the highest IgG1 expression. More strikingly, while we found an overall increase in PCs in responders compared to non-responders, there was a significantly higher enrichment of IgG1-high PC clusters in ICB responders compared to non-responders. Single-cell BCRseq on five patients (2 responders and 3 non-responders) revealed that the tumor-derived Bmems and PCs in responders were more clonally expanded than those from non-responders. Furthermore, we observed that while the clonally expanded B cells in non-responders were dominated by IgA or IgM isotypes, the clonally expanded B cells in responders were exclusively IgG1 or IgG3. Finally, we detected peripheral IgG antibodies against at least one tumor-antigen in our panel in 63% of the responders—which were mostly dominated by IgG1—whereas only 22% of non-responders had detectable IgG titers against any of the tumor antigens.

Conclusions HCC responders to ICB had B cell responses skewed towards an IgG1 phenotype, and the presence of anti-tumor IgG1 antibodies correlated with ICB response.

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Trial Registration NCT03916627

REFERENCES

Ethics Approval This study was approved by Icahn School of Medicine at Mount Sinai’s institutional review board, approval numbers 19-0246 and 19-06-061-05. All study participants gave informed consent before taking part in this study.