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SINGLE CELL IMMUNOLOGIC DISSECTION OF CHECKPOINT INHIBITOR HEPATITIS AND AUTOIMMUNE HEPATITIS REVEALS INSIGHTS INTO IMMUNE TOLERANCE IN THE HUMAN LIVER

¹Molly Thomas*, ¹Tos Chan, ¹Neal Smith, ¹Marc Sherman, ¹Swetha Ramesh, ¹Alice Tirard, ¹John McGuire, ¹Mazen Nasrallah, ¹Kasidet Manakongtreecheep, ¹Jessica Tantivit, ¹Leyre Zubiri, ¹Dejan Juric, ¹Ryan Sullivan, ¹Genevieve Boland, ¹Georg Lauer, ²Nir Hacohen, ¹Kery Reynolds, ¹Chloe Villani. ¹MGH, Boston, MA, USA; ²Broad Institute, Cambridge, MA, USA

Background The emergence of monoclonal antibodies targeting PD-1 and CTLA-4 to treat solid tumors has revolutionized the field of immuno-oncology. However, immune checkpoint blockade (ICB) is limited by frequent immune-related adverse events. ICB-induced hepatic toxicity (irHepatitis) occurs in approximately 1-17% of patients. While these adverse events are usually mild, they often delay cancer treatment and require initiation of immunosuppressive therapy, which may compromise anti-tumor immune responses. irHepatitis shares clinical and histologic features with autoimmune hepatitis (AIH). As such, the study of irHepatitis is important not only for the care of oncology patients but also for the understanding how immune tolerance is lost across a spectrum of inflammatory liver diseases.

Methods To characterize the cellular and molecular pathways underpinning hepatic injury in irHepatitis, we used single-cell and single-nuclei RNA sequencing (scRNAseq/snRNAseq) with paired T-cell receptor (TCR) and B-cell receptor (BCR) sequencing to characterize ~300,000 cells from the liver and blood of 23 patients – 9 patients with irHepatitis, 4 patients with AIH, 3 controls on ICB, and 7 controls not on ICB. irHepatitis was defined by a hepatocellular or cholestatic rise in LFTs often with centrilobular histiocytic liver injury requiring treatment with steroids. Control patients had drug-induced liver injury, hepatic steatosis, non-alcoholic steatohepatitis, primary biliary cirrhosis, or venous outflow obstruction that did not require immunosuppressive therapy.

Results In irHepatitis we detected liver T cells expressing *CXCL13* and expanded cycling and cytotoxic CD8 T cells spanning effector to exhausted phenotypes. TCR repertoire analysis demonstrated clonal expansion of CD8 T cell subsets specific to irHepatitis. Parallel analysis of tissue immune cells from patients with AIH and irHepatitis enabled the identification of cell types and states both common and unique to each type of immune-mediated liver injury. For all patients, matched blood samples were also analyzed by scRNAseq to determine how cellular and transcriptional signatures in the liver tissue microenvironment were mirrored in circulating immune cells. Lastly, analysis of hepatocytes, cholangiocytes, and mesenchymal cells revealed specific inflammatory signatures in irHepatitis and AIH that suggested significant liver parenchymal dysfunction.

Conclusions In defining the cellular and transcriptional programs that are altered in irHepatitis, we have identified novel pathways that could be therapeutically targeted to treat liver inflammation in this context and have determined how PD-1 and CTLA-4 signaling may contribute to immune tolerance in the liver.

Ethics Approval This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Boards (DFCI/HCC 11-181 and 13-416, Mass General Brigham 2010P001242).

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