Despite recent advances in our understanding of the cellular heterogeneity of the human liver, the role of liver resident lymphocytes and in particular, intrahepatic T cells remains an important open question with implications in liver health and disease. Despite early reports of the liver promoting T cell apoptosis, T cells are increasingly understood to be functional in the liver. However, the functions of intrahepatic T cells are altered in disease states such as suppression of T cell function during endotoxin challenge, which may contribute to delayed antigen clearance. Studies such as these underscore the phenotypic complexity of intrahepatic T cells, which remains to be fully examined, a topic Koh et al., address through a multi-omic approach with extensive functional validation in their paper in this issue of *Journal of Hepatology* (Fig. 1).

To perform these examinations, the authors obtained liver perfusates and biopsies from healthy living donor liver transplant donors and transplant recipients being transplanted for hepatitis B virus (HBV)-associated chronic liver disease. The authors employed cellular indexing of the transcriptomes and epitopes by sequencing (CITE-seq) analysis along with T cell receptor sequencing (TCR-seq) to examine the transcriptional programs and clonotypic diversity of liver sinusoidal lymphocytes in healthy and HBV-related disease, validating their transcriptional findings with ex vivo phenotypic and functional experiments. This approach revealed a distinct sinusoidal CD56hiCD161-CD8+ T-cell population characterized by natural killer cell (NK)-like activation, including the expression of perforin, granzyme, IFN-γ and the potential to degranulate. This population, which was enriched in the liver versus the blood, was expanded in HBV-associated liver disease and exerted NKG2C-mediated NK-like effector functions in the absence of TCR stimulation. Koh and colleagues further showed that these intrahepatic CD56hiCD161 CD8+ T-cells possessed a restricted TCR repertoire and exhibited enhanced responses to innate cytokines, particularly interleukin (IL)-12/IL-18 and IL-15. The authors assert that these liver-resident CD56hiCD161 CD8+ T-cells may share features with virtual memory T cells (TVM), recently described in mice. Importantly, these liver sinusoidal CD56hiCD161 CD8+ T cells exerted NK-like, TCR-independent cytotoxic activity through NKG2C ligation whereas previous reports demonstrated that the NK receptor, NKG2D, served only as a co-stimulatory receptor for TCR-mediated activation.

An important analysis from this study was a formal comparison of immune cells isolated from liver perfusates and immune cells isolated from enzyme-digested liver biopsy tissue. To perform this comparison, the authors isolated liver sinusoidal mononuclear cells from matched liver perfusates and biopsy tissues obtained from 20 individuals with or without HBV-associated chronic liver disease. The authors then comprehensively compared cellular compositions and phenotypes between liver sinusoidal and intrahepatic immune cells. In terms of cellular composition, the authors found a significant correlation in the percentages of TEM, TEMRA, and CD56hiCD161 cells between liver sinusoidal and intrahepatic CD8+ T cells. Regarding phenotype, the authors found that the frequency of perforin+ cells, granzyme B+ cells, and granulysin+ cells was similar between the liver sinusoidal CD56hiCD161 CD8+ T cells and the intrahepatic CD56hiCD161 CD8+ T cells. This is an important evaluation that reinforces the notion that liver sinusoidal T cells reflect that of the intrahepatic immune environment.

Regarding activation of intrahepatic T cells, these data add to a growing body of literature that intertwines antigen-specific, TCR-mediated activation with bystander T cell activation. Antigen-specific tolerance occurs when naive T cells are primed in the absence of inflammation. However, inflammation that activates antigen presenting cells and provides the third signal for effective T cell priming also induces bystander effector T cell activation. IL-15 and transforming growth factor (TGF)-β coordinate to differentiate CD8+ T cells towards a tissue resident phenotype, capable of producing high levels of IL-2, a required signal for Kupffer cell cross-presentation in HBV.
cells are highly responsive to innate cytokines, particularly interleukin (IL)-12/IL-18 and IL-15. Disease and exert NKG2C-mediated NK-like effector functions with a restricted T cell receptor (TCR) repertoire and weak TCR engagement. These liver sinusoidal T cells express perforin, granzyme, interferon (IFN)-γ and the potential to degranulate. These cells are expanded in Hepatitis B virus (HBV)-associated liver disease and exert NKG2C-mediated NK-like effector functions with a restricted T cell receptor (TCR) repertoire and weak TCR engagement. These liver sinusoidal T cells are highly responsive to innate cytokines, particularly interleukin (IL)-12/IL-18 and IL-15.

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Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

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A.J.G and S.A.M contributed equally to this work.

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