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Distinct immune landscapes in Autoimmune vs. Checkpoint Inhibitor-Associated Hepatitis revealed by spatial profiling

Immune-related adverse events (IRAEs) to checkpoint inhibitor therapy can be life-threatening, yet their underlying mechanisms remain poorly understood. It is often presumed that the involved cellular mechanisms bear similarities with spontaneous autoimmune diseases. In this work, we compared the intrahepatic immune landscape of checkpoint-inhibitor-associated hepatitis (ICI-Hep) with that of spontaneous autoimmune hepatitis (AIH) using spatial single-cell and spatial transcriptomic analyses of inflamed liver tissue from affected patients.

Our findings reveal fundamentally distinct immune landscapes in ICI-Hep and AIH. ICI-Hep is characterized by pronounced interactions between activated cytotoxic $CD8^+$ T cells and activated myeloid cells—features not seen in AIH, which instead shows an enrichment of exhausted and tissue-resident T cells alongside B cells. Notably, the pathognomonic immune cell interactions in ICI-Hep involve active mTOR signaling. Inhibition of mTOR led to reduced activation of $CD8^+$ and myeloid cells and resulted in clinical improvement of liver inflammation in patients.

These results highlight distinct cellular pathomechanisms in IRAEs and establish mTOR signaling trageting as a rational therapeutic option for severe ICI-Hep.

Preferred type of presentation

Poster Presentation only

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