Human liver CD14⁺CD8⁺ T cells are enriched in cellular immune responses to hepatitis B virus and cancer

Pallett LJ. *et al.* Tissue CD14⁺CD8⁺ T cells reprogrammed by myeloid cells and modulated by LPS. Nature 2023.
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Background

The liver mounts swift immune responses despite tolerating high levels of pathogens and their products, like lipopolysaccharide (LPS) from the gut. Elucidating mechanisms of this plasticity led the authors of this study to examine a tissue-resident population of memory CD8⁺ T cells that co-stain for CD14, a co-receptor of bacterial LPS typically expressed by myeloid cells like macrophages.

Study Description

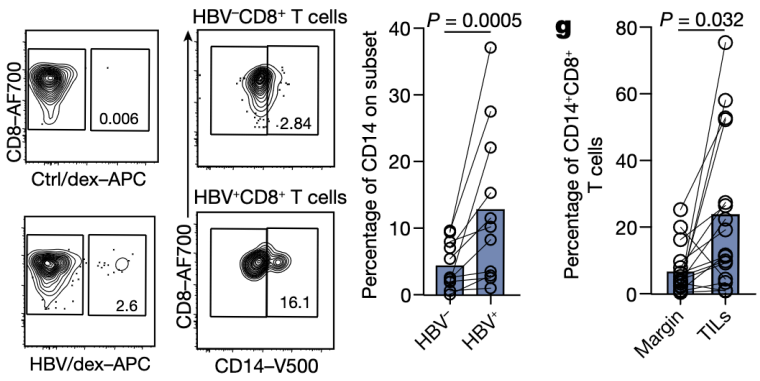
The authors systematically characterized the CD14⁺CD8⁺ T cells. Spatial colocalization to CD14^{high} myeloid cells in liver sections, co-culture experiments, RT-qPCR, and single-cell transcriptomics corroborated that membrane material including the entire CD14-TLR4-MD-2 complex is transferred from myeloid to CD8⁺ T cells. Transfer is facilitated by LPS from dead *Escherichia coli* and appears to "instruct" recipient T cells to be highly activated and immunomodulatory. To examine their role in disease, the authors quantified CD14⁺CD8⁺ T cells among HBV-specific intrahepatic leukocytes extracted from infected livers and tumor-infiltrating leukocytes (TILs) isolated from resected hepatocellular carcinoma tissue.

Results

- A panel of MHC Dextramer® reagents loaded with different HBV antigens revealed a two-fold enrichment of CD14⁺CD8⁺ T cells relative to the residual global CD8⁺ T cell population in tissue samples from HBV-infected livers.
- Similarly, TILs from resected hepatocellular carcinoma (HCC) samples included three times more CD14⁺CD8⁺ T cells compared to paired unaffected liver margin samples.
- *In vitro*, acquisition of CD14 correlated with enhanced effector function, including increased secretion of IL-2, IFNγ, TNF, and CD10 based on flow cytometry measures.

Fig.1. Infection and cancer-associated enrichment of CD14⁺CD8⁺ T cells

Flow cytometry data shows enriched CD14-staining of HBV-specific T cells relative to T cells binding a control Dextramer® Reagent (dex) loaded with an HBV irrelevant epitope. Charts summarize the presence of CD14⁺CD8⁺ T cells among lymphocytes in HBV-infected and HCC liver tissues.



Conclusions

- A subset of T cells in the human liver that acquire CD14 and other prototypic markers from myeloid cells show strong immunoregulatory effector function and are enriched in diseased tissues.
- Loaded with HBV epitopes, a panel of Dextramer® reagents delivered the sensitivity and specificity needed to quantify this low-abundance and highly variable population subset.
- Myeloid co-cultures can be used to generate TCR gene-edited T cells with superior immunotherapeutic potential for adoptive cell therapy.