Liver and kidney have tissue-specific CD8 T cell subpopulations

Since cancer has become the second leading cause of death globally [1], their effective clinical treatments have been an impending need worldwide. Fortunately, the invention of immune checkpoint blockade (ICB) [2], [3], [4] has provided effective treatments in the cancer range of cancers [4]. Nevertheless, although the efficacy of ICB has been attributed to CD8 T cells, the underlying mechanism remains poorly understood. In recent years, with the clinical application of ICB, the distinct effects of ICB on the treatment of different cancer types and the tissue-specific complications of ICB (immune-related adverse events, IRAE) have been widely reported [2, 3], in allusion to the widely reported association between tissues and ICB effects, a comprehensive comparison of tissue-infiltrating CD8 T cells is necessary for ICB-related research.

Figure 1. Immune checkpoint blockade (ICB) and immune-related adverse events (ICREs).

(A) Various ICB-based medicines have been approved for the clinical treatment of a broad range of cancers [4].

(B) The functional mechanism of ICB. Tumour cells induce the overexpression of immune checkpoints in CD8 T cells, which efficiently hinders the recognition of tumour cells and the elimination of tumour cells. Through blocking immune checkpoints with antibodies, ICB therapies restore immune recognition by CD8 T cells, reactivating their cytotoxic activity against tumour cells.

(C) The occurrence of IRAE is mainly concentrated in intestine, liver and skin of patients.

Our Goal: To explore tissue-specific patterns of CD8 T cells through comprehensively characterise and compare infiltrating CD8 T cells from different tissues.

Challenge & Methodology

The main challenge of CD8 T cell characterisation and comparison is caused by the high heterogeneity of tissue-infiltrating CD8 T cells. The differentiation of CD8 T cells in peripheral tissues is a complicated process, causing that tissue-infiltrating CD8 T cells are mainly composed of four cell types, including naive, effector, memory and exhausted CD8 T cells [5]. Aiming to characterise the highly heterogeneous CD8 T cells, single-cell RNA sequencing (scRNA-seq) was performed in our study. We isolated tissue-infiltrating CD8 T cells from different tissues of Fas-gene knock-out mice, including intestine, kidney, liver, lymph nodes, lung, PBMC, spinal cord and spleen, then used them for 10x Chromium scRNA-seq. After the integration of data from 8 tissues, the cells were clustered into 12 subpopulations with their specific cell type for characterisation.

Figure 2. Using single-cell RNA sequencing (scRNA-seq) to characterise the highly heterogeneous CD8 T cells.

(A) Peripheral CD8 T cells are highly heterogeneous due to their complicated differentiation process [5].

(B) The optimal workflow of tissue-infiltrating CD8 T cells isolation used in this research.

(C) Trajectory analysis reveals the tissue-specific cell type constitutions of intestine and kidney.

Figure 3. Liver and kidney have tissue-specific CD8 T cell subpopulations.

(A) Dot plot showing the tissue percentages in each cluster. Each column represents a tissue, and each row represents a cluster. The sizes of the dots represent the percentage of tissue-specific cells in a specific cluster. The coloured dots correspond to the graph-based clusters to which they belong.

(B) T-SNE plot of the graph-based clusters with the tissue-specific clusters labelled.