Single-cell Genomics Study of Fontan-associated Liver Disease

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Abstract

The Fontan circulation (FC) is the current strategy of care for single ventricle congenital heart disease (SVCHD), a unique congenital cardiac anomaly in which there is only one functional ventricle/pumping chamber. It is estimated that there are approximately 80,000 survivors of this procedure alive today worldwide. Although operative survival has improved over the years, it is now evident that these surviving SVCHD patients are facing new life-threatening challenges: severe complications resulting from the Fontan operation, including one of the most evident consequences---hepatic fibrosis, which is now recognized as Fontan-Associated Liver Disease (FALD). Unfortunately, the fundamental mechanisms underlying FALD remain little understood.

In this study, single-nucleus RNA-ATAC sequencing (snRNA-ATAC-seq) is used to determine cell-type specific transcriptional and epigenetic changes from the same cell in normal and early-stage Fontan livers. Fontan livers exhibit cell type-specific gene expression changes, mostly affecting central hepatocytes, but also significantly in endothelial cells, HSC and cholangiocytes. Genes involved in peroxisome metabolism, liver detoxification of various metabolic intermediates, removal of reactive oxygen species (ROS) are highly upregulated in central hepatocytes in Fontan livers. Therefore, FALD is not only a hepatic fibrosis disease, but also features severe dysregulation of liver metabolism.