Researchers discover biology behind Fontan-operation-associated liver disease

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As patients with congenital heart diseases live longer, researchers are attempting to understand some of the other complications they may face as they age. A team from Children's Hospital of Philadelphia (CHOP) used state-of-the-art technologies to understand the underlying biology of Fontan-associated liver disease (FALD).

The findings, published in *Science Translational Medicine*, reveal unprecedented insights into how the disease develops and potential therapeutic targets for future treatment options.

The Fontan operation is the current standard of care for single-ventricle congenital heart disease. In this surgery, blood carried by the inferior vena cava, a vein that carries deoxygenated blood from the lower body into the heart, is channeled directly into the pulmonary arteries.

After this operation, all the deoxygenated blood from the body is delivered to the lungs but without the benefit of a pump, resulting in the potential for venous congestion. Approximately 80,000 people worldwide have had a Fontan procedure.

The Fontan circulation (FC)—when the heart receives oxygenated blood from the lungs and pumps it to the body—is life-sustaining for individuals with single ventricle type of congenital heart disease but comes with many potential challenges. Patients with FC can face potentially life-threatening complications from early-onset hepatic fibrosis, now known as FALD.

As more patients undergo the Fontan surgery for single-ventricle congenital heart disease, FALD has become a more recognized problem.

Little information exists on FALD, yet it is distinct from other forms of liver disease, which is why researchers at CHOP wanted to understand the basic biology that could lead to better treatment options and improve these patients' quality of life.

"As our expertise with Fontan surgery improves and the number of survivors increase, we want to be able to offer these patients an improved quality and duration of life," said study co-author Jack Rychik, MD, Director of the Fontan Rehabilitation, Wellness, Activity and Resilience Development (FORWARD) Program at CHOP, one of the first multidisciplinary clinics established in the world focused on Fontan circulation specific care.

"This study allowed us to achieve a deeper understanding of Fontan-associated liver disease, and this translational research is something we hope leads us to studies that cure and improve the outcomes for patients born with half a heart."

In the study, researchers generated the first complete atlas of RNA and epigenetic statuses of human FALD at a single-cell level by studying tissues samples from patients with early-stage disease. The atlas revealed profound cell-type specific changes in livers with Fontan circulation. The most significant changes were observed in central hepatocytes, cells that play a key role in proper liver function.

The researchers found that these hepatocytes had significant metabolic reprogramming that preceded the activation of other cells closely associated with FALD, suggesting that central hepatocytes are a key part in understanding the origins of the disease.

The researchers also identified how Activins A and B, signaling molecules involved in several key developmental processes, may play a role in the development of fibrosis, or the thickening or scarring of

tissue that in this case can contribute to FALD, suggesting that they may serve as potential therapeutic targets.

"Our findings make the case that there may be some way for us to blunt the process that leads to scarring at the cellular level," said senior study author Liming Pei, Ph.D., an associate professor of Pathology and Laboratory Medicine at CHOP and member of the CHOP Cardiovascular Institute.

"The pathways we identified are worth studying in additional models and confirming whether that information could lead to the discovery of new therapeutic options."

More information: Po Hu et al, Single-cell multiomics guided mechanistic understanding of Fontan-associated liver disease, *Science Translational Medicine* (2024). DOI: 10.1126/scitranslmed.adk6213. www.science.org/doi/10.1126/scitranslmed.adk6213

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