Researchers produce iPSC model to better understand genetic lung/liver disease

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Using patient-derived stem cells known as induced pluripotent stem cells (iPSC) to study the genetic lung/liver disease called alpha-1 antitrypsin (AAT) deficiency, researchers have for the first time created a disease signature that may help explain how abnormal protein leads to liver disease.

The study, which appears in *Stem Cell Reports*, also found that liver cells derived from AAT deficient iPSCs are more sensitive to drugs that cause liver toxicity than liver cells derived from normal iPSCs. This finding may ultimately lead to new treatments for the condition.

IPSC's are derived from the donated skin or blood cells of adults and, with the reactivation of four genes, are reprogrammed back to an embryonic stem cell-like state. Like embryonic stem cells, iPSC can be differentiated toward any cell type in the body, but they do not require the use of embryos. Alpha-1 antitrypsin deficiency is a common genetic cause of both liver and lung disease affecting an estimated 3.4 million people worldwide.

Researchers from the Center for Regenerative Medicine (CReM) at Boston University and Boston Medical Center (BMC) worked for several years in collaboration with Dr. Paul Gadue and his group from Children's Hospital of Philadelphia to create iPSC from patients with and without AAT deficiency. They then exposed these cells to certain growth factors in-vitro to cause them to turn into liver-like cells, in a process that mimics embryonic development. Then the researchers

studied these "iPSC-hepatic cells" and found the diseased cells secrete AAT protein more slowly than normal cells. This finding demonstrated that the iPSC model recapitulates a critical aspect of the disease as it occurs in patients. AAT deficiency is caused by a mutation of a single DNA base. Correcting this single base back to the normal sequence fixed the abnormal secretion.

"We found that these corrected cells had a normal secretion kinetic when compared with their diseased, parental cells that are otherwise genetically identical except for this single DNA base," explained lead author Andrew A. Wilson, MD, assistant professor of medicine at Boston University School of Medicine and Director of the Alpha-1 Center at Bu and BMC.

They also found the diseased (AAT deficient) iPSC-liver cells were more sensitive to certain drugs (experience increased toxicity) than those from normal individuals. "This is important because it suggests that the livers of actual patients with this disease might be more sensitive in the same way," said Wilson, who is also a physician in pulmonary, critical care and allergy medicine at BMC.

According to Wilson, while some patients are often advised by their physicians to avoid these types of drugs, these recommendations are not based on solid scientific evidence. "This approach might now be used to generate that sort of evidence to guide clinical decisions," he added.

The researchers believe that studies using patient-derived stem cells will allow them to better understand how patients with AAT deficiency develop liver disease. "We hope that the insights we gain from these studies will result in the discovery of new potential treatments for affected patients in the near future," said Wilson.

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