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Successful correction of genetic mutation in stem cells offers promise for lung diseases

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For the first time, researchers have developed a way to coax pluripotent stem cells into a specific type of mature lung cell called "alveolar epithelial type II cells" (AEC2s) and to correct a mutant gene whose dysfunction in these cells is known to cause respiratory distress in infants.

The findings, which appear in *Cell Stem Cell*, will make it easier to study lung diseases like neonatal respiratory distress, COPD and interstitial lung diseases, caused by dysfunctional AEC2s, which until now were unable to survive and multiply long enough in cell culture to be studied or genetically corrected.

AEC2s are the key cells that act to maintain lung air sacs in both infants and adults. They are responsible for responding to lung injury and secreting a substance called "pulmonary surfactant" that helps keep the lungs open. It is believed that dysfunction of these specific cells leads to the development of many poorly understood alveolar lung diseases (diseases of the air sacs in the lungs) and is the main culprit responsible for respiratory distress in babies born prematurely before AEC2s are ready to produce surfactant. Importantly the new findings demonstrate the capacity of stem cell-derived AEC2s in culture to produce surfactant, a long sought-after milestone not previously achieved.

This discovery now allows scientists to isolate AEC2s from pluripotent stem cells that can be engineered from any patient. The stability of these cells in culture also enables scientists to create models for understanding

the diseases they underlie and to develop new gene, cell and drug therapies for those diseases.

"Now that we have generated a source of these cells and shown that they can model alveolar diseases in culture, this should make it much easier to study a variety of related diseases, possibly leading to a better understanding of these diseases and hopefully to more mechanism-specific therapies for otherwise incurable diseases," explained first author Anjali Jacob, an MD/PhD student at Boston University School of Medicine (BUSM) in the department of Molecular and Translational Medicine.

Testing the Science

Using induced pluripotent stem cells (iPSCs), the researchers were able to generate and purify induced alveolar epithelial type II cells (iAEC2s) in 3D structures called "alveolospheres." They then went on to prove these alveolospheres were able to proliferate over a period of months generating millions of descendants in culture from each purified starting cell.

After establishing the ability to generate and maintain these cells, the researchers took a skin sample from a child with a mutation in the "SFTPB" gene known to cause AEC2 dysfunction and neonatal respiratory distress. They then engineered induced pluripotent stem cells (iPSCs) from the child's skin cells and separated the cells into two groups, one in which they left the cells as they were with the known mutation and one in which they corrected the mutation using gene editing. When they compared alveolospheres generated from the two groups, they found that the cells whose genes had been edited to correct the "SFTPB" mutation had restored function compared to the non-edited cells, and no longer had the deficiencies that were thought to be underlying the child's lung disease. "This shows that "iPSC-derived

alveolospheres represent a faithful model for real human lung disease in an easier-to-study format in cell culture," said corresponding author Darrell Kotton, MD, the David C. Seldin Professor of Medicine at BUSM and Director of the BU/Boston Medical Center (BMC) Center for Regenerative Medicine (CReM).

The researchers believe this study represents an important step towards the future regeneration of diseased alveoli through cell based therapy. "Someday, we hope we can develop approaches that can use these cells to replace dysfunctional alveolar cells in human lungs," added Kotton.

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