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Researchers develop novel gene / cell therapy approach for lung disease

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Researchers developed a new type of cell transplantation to treat mice mimicking a rare lung disease that one day could be used to treat this and other human lung diseases caused by dysfunctional immune cells.

Scientists at Cincinnati Children's Hospital Medical Center report their findings in a study posted online Oct. 1 by *Nature*. In the study, the authors used macrophages, a type of immune cell that helps collect and remove used molecules and cell debris from the body.

They transplanted either normal or gene-corrected macrophages into the respiratory tracts of mice, which were bred to mimic the hereditary form of a human disease called hereditary pulmonary alveolar proteinosis (hPAP). Treatment with both normal and gene-corrected macrophages corrected the disease in the mice.

"These are significant findings with potential implications beyond the treatment of a rare lung disease," said Bruce Trapnell, MD, senior author and a physician in the Division of Neonatology and Pulmonary Biology at Cincinnati Children's. "Our findings support the concept of pulmonary macrophage transplantation (PMT) as the first specific therapy for children with hPAP"

"Results also identified mechanisms regulating the numbers and phenotype of macrophages in the tiny air sacs of the lungs (called alveoli) in health and disease," said Takuji Suzuki, MD, PhD, the study's first author and a scientist in the Division of Neonatology and

Pulmonary Biology at Cincinnati Children's.

Suzuki and Trapnell discovered hPAP at Cincinnati Children's and first reported it in 2008. In hPAP, the air sacs become filled with surfactant, a substance the lungs produce to reduce surface tension and keep the air sacs open. Children with hPAP have mutations in the genes of GM-CSF receptor alpha or beta (CSFR2RA or CSFR2RB). These mutations reduce the ability of alveolar macrophages to remove used surfactant from the lungs of these children.

The used surfactant builds up in the lungs, filling the alveoli and causing difficult breathing or respiratory failure. The only current treatment for these children is whole-lung lavage, an invasive lung-washing procedure performed under general anesthesia. Although the procedure works, it is temporary, must be repeated frequently, and creates quality of life issues for affected children.

Previous studies have tested bone marrow transplant (BMT) to treat mouse models of hPAP – which involves myeloablation, or using radiation and/or chemotherapy to destroy existing bone marrow. BMT was effective in mice, but in humans resulted in death before the new bone marrow grew and expanded (called engraftment) in treated patients.

Trapnell and Suzuki were prompted to test the novel macrophage transplantation therapy by studies showing that resident macrophage populations (such as those residing in the lung) can self-maintain without the cells having to regenerate directly from the bone marrow. Results showed that naturally healthy macrophages and gene-corrected macrophages worked equally well in correcting the disease in the mice.

In mice mimicking hPAP that lacked expression of the mouse gene - Csf2rb, the researchers used a viral vector to deliver a correct version of

Csf2rb to abnormal alveolar macrophages taken from the animals. The gene-corrected cells were then administered back to the mice by direct instillation into the lungs.

The researchers report that treatment was safe, well tolerated by the animals, and that one administration corrected the lung disease, normalized disease-related biomarkers and prevented disease-specific mortality for at least one year.

Although the gene/cell therapy strategy was highly successful in laboratory mice, the authors stressed that additional research and testing are needed before the therapy could be tested in humans. They must still confirm the precise pharmacokinetics, or how the body processes the therapy after it is administered. Also needed is data to help determine appropriate dosage levels and therapeutic duration following treatment. The pre-clinical studies needed are now in progress and planning for the human studies is underway.

More information: Pulmonary macrophage transplantation therapy, *Nature*, DOI: 10.1038/nature13807

Provided by Cincinnati Children's Hospital Medical Center