Pulmonary alveolar microlithiasis: Mouse model offers new insights into rare lung disease

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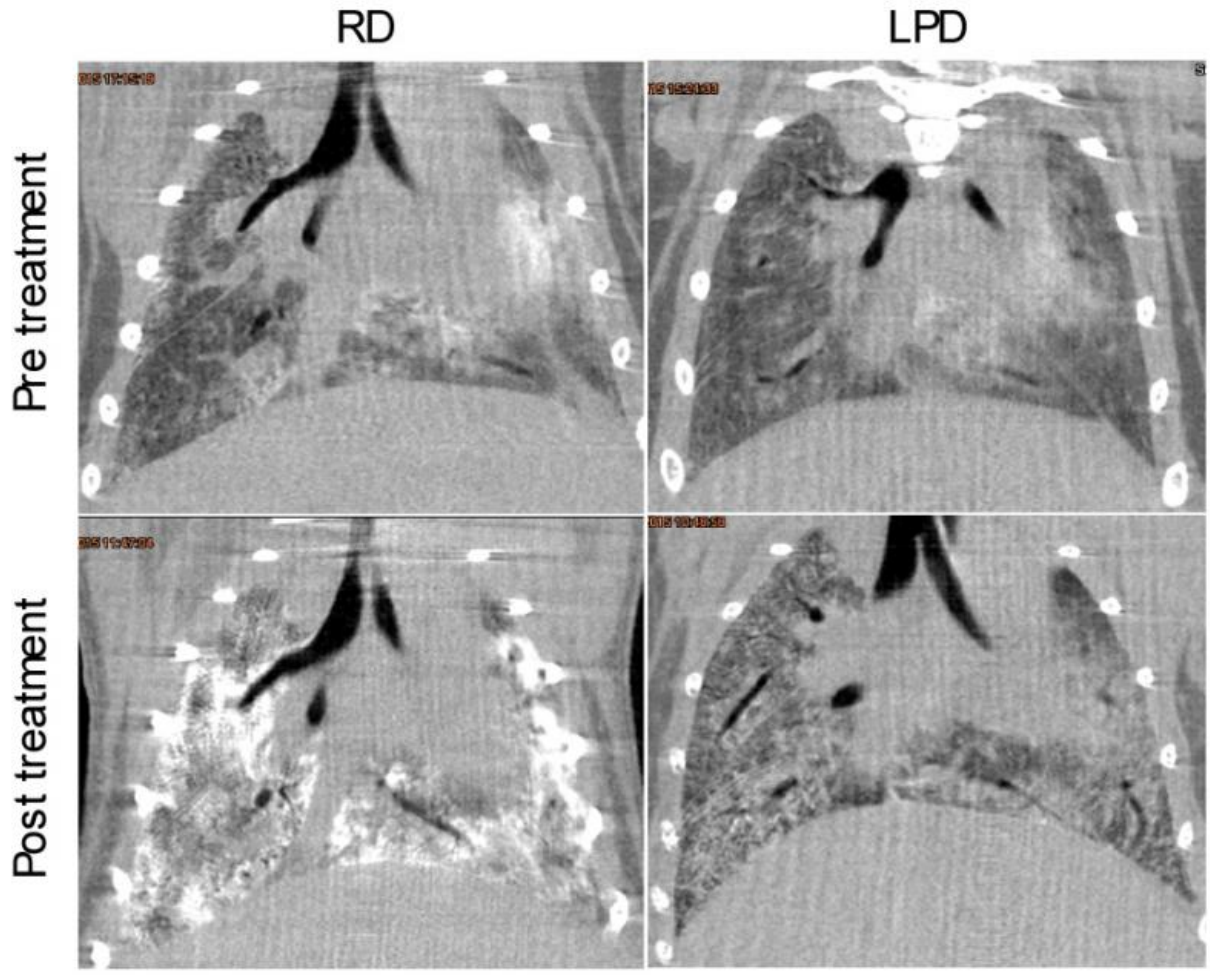

Micro–computed tomography imaging before and after challenging 3-week-old mice with regular diet (RD) or low-phosphate diet (LPD) for 2 months. LPD prevents and improves microlith accumulation. Credit: Saito et al., Science

New research from an investigative team at the University of Cincinnati (UC) has identified biomarkers and potential therapeutic approaches that may hold the key to treating pulmonary alveolar microlithiasis (PAM), a rare lung disease.

Published online Nov. 11, 2015, in *Science Translational Medicine*, the research is led by Atsushi Saito, PhD, a former postdoctoral fellow at UC, Nikolaos Nikolaidis, PhD, a senior research assistant at UC, and Frank McCormack, MD, Taylor Professor and Director of the Division of Pulmonary, Critical Care and Sleep Medicine and senior author on the article.

"Pulmonary alveolar microlithiasis (PAM) is a human disease in which small stones accumulate in the alveolar air sacs of the lung," explains McCormack. "The genetic basis of the disease was reported about eight years ago by Japanese and Turkish investigators, who found that DNA mutations in the gene SLC34A2 resulted in the loss of a cellular pump known as Npt2b that removes phosphate from the airspaces.

"As a result, calcium and phosphate rise in the alveolar sacs, leading to the formation of microliths that induce chronic inflammation. Scarring and respiratory failure generally occurs in middle age or later," says McCormack.

Researchers developed the model to explore human therapies for the disease. The team found that the animals with mutations in SLC34A2 developed abundant stone formation, followed by lung injury and inflammation, which were reflected by elevations in certain key serum markers, says McCormack.

To determine if the proteins in serum might be useful biomarkers in humans, the team collected blood from patients in Croatia, Turkey, Spain, Japan and the United States through the Cincinnati-based Rare Lung Disease Consortium, says McCormack. The consortium is supported by the National Institutes of Health's National Center for Advancing Translational Sciences (NCATS) through its Rare Diseases Clinical Research Network (RDCRN).

"The NCATS goal for the RDCRN program is to advance medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrollment and data sharing," says Rashmi Gopal-Srivastava, PhD, RDCRN program director, NCATS. "This enables scientists from multiple disciplines at hundreds of clinical sites around the world such as the Rare Disease Lung Consortium to work together with patient advocacy groups to study more than 200 rare diseases."

UC researchers learned that certain cytokines and surfactant proteins in serum tracked with the burden of stones in the lung, suggesting they may become useful tools for following disease progression and treatment response in patients, explains McCormack.

A surprising finding was that stone removed from the lung readily dissolved in EDTA, a calcium-binding molecule that is a component of many detergents, and is used as a treatment for heavy metal poisoning, says McCormack.

"Washing the lungs with an EDTA-containing solution reduced the burden of stones in airspaces," says McCormack. "This finding could translate into a therapy for humans if toxicity studies demonstrate that the approach is safe."

A low-phosphate diet was also found to prevent stone development in

the lung and even to reverse lung calcification in the animals, explains McCormack. However, phosphate-restricted diets must be tested in trials before they can be recommended because they can cause other medical problems such as rickets if not properly administered. Other strategies for restoring normal phosphate balance in the lung include inserting a gene for a working phosphate pump back into the cells of the lung using viral vectors, says McCormack.

"This study demonstrates how discovering the causes of these rare lung diseases not only can inform us how the lung normally functions, but can also lead us to potential therapeutic interventions for these rare and often lethal lung diseases," says James Kiley, PhD, Director of the Division of Lung Diseases at NHLBI.

Although human trials are a few years way, UC's research offers some hope to patients like Kathleen Falco, 65, who resides in Riverhead, NY. She's known she's had some lung disorder since 1977, when she was mistakenly diagnosed with sarcoidosis after seeking treatment for a respiratory infection. It wasn't until the year 2000 that an astute physician diagnosed her with pulmonary alveolar microlithiasis.

"At 27, I felt like there was nothing wrong with me," says Falco. "As I got older, it started to take a toll in my 40s. I was limited in what I could do."

Three years ago, the symptoms intensified and she developed shortness of breath and now requires a continuous supply of supplemental oxygen. Her mobility was also restricted.

"I can't do the daily activities I enjoyed once upon a time, like walking and playing golf," says Falco. "I started losing weight and about two years ago, I realized nobody will help me but me. I started making phone calls and searching the Internet for information."

That's when Falco reached out to the National Institutes of Health (NIH) for help, who invited her to come to the institute for three days of interviews, tests and examinations. The NIH researcher was able to connect Falco with McCormack during the fall of 2014.

"He told me he had something going on and maybe within a year or two there would be a clinical trial," says Falco, a former administrative assistant at Stony Brook University.

Explaining her challenges with PAM is so difficult, says Falco.

"If it is too hot I can't breathe. If it gets too cold I can't breathe," says Falco. "I would say the spring and the fall are the better months. It's very hard to explain what's wrong. There are no support groups to share this with. Not being able to do the things I once loved creates frustration and anger at times. I am 65 and praying for a miracle."

McCormack says rare disease research can reveal surprising insights into the fundamental biology of the lung.

"Studies of the PAM mouse model have already revealed a potential role for phosphate in the regulation of surfactant balance in the lung and have attracted the interest of cystic fibrosis scientists interested in exploring the possible interaction between Npt2b and the defective chloride channel in that disease," explains McCormack.

More information: "Modeling pulmonary alveolar microlithiasis by epithelial deletion of the Npt2b sodium phosphate cotransporter reveals putative biomarkers and strategies for treatment," stm.sciencemag.org/lookup/doi/ … scitranslmed.aac8577