Severe asthma fails to respond to mainstay treatment

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Children with asthma use inhalers to relieve some of their symptoms, which include coughing, wheezing, chest tightness and shortness of breath. Credit: Tradimus / Wikimedia commons / CC BY-SA 3.0

The immune response that occurs in patients with severe asthma is markedly different than what occurs in milder forms of the lung condition, according to researchers from the University of Pittsburgh School of Medicine. Those unique features could point the way to new treatments, they said in an article published online today in the *Journal*

of Clinical Investigation (*JCI*).

People with severe asthma, in which the airways become inflamed and constrict to impair breathing, do not get better even with high doses of corticosteroids, the mainstay of treatment for typical asthma, explained Anuradha Ray, Ph.D., professor of medicine, Pitt School of Medicine.

"About 10 percent of asthma patients have a severe form of the disease, but they account for up to half of asthma costs in the U.S. and Europe," Dr. Ray said. "That's because these patients frequently need to go to the emergency room or be hospitalized when they have an acute asthma episode."

For the study, conducted as part of the doctoral thesis of Mahesh Raundhal, a graduate student in the laboratory of Prabir Ray, Ph.D., Pitt professor of medicine and co-senior author, the research team examined lung cell samples obtained from patients also participating in the Severe Asthma Research Program (SARP), a National Heart, Lung, and Blood Institute of the National Institutes of Health-sponsored program to improve the understanding of severe asthma. Sally Wenzel, M.D., director of the University of Pittsburgh Asthma Institute of UPMC, serves as the Pitt SARP principal investigator.

Researchers observed that the immune cells, called CD4 T-cells, in the airways of severe asthmatics secreted different inflammatory proteins than those in mild disease, particularly interferon gamma. The analysis of human samples helped them to develop a mouse model of the disease by introducing an allergen and a bacterial product to induce an immune profile and airway hyper-reactivity that were poorly controlled by corticosteroids, comparable to human severe asthma patients.

When they subjected mice that lacked the interferon gamma gene to the severe asthma model, they found that the mice could not be induced to

develop severe asthma. Using computer modeling to identify links between interferon gamma and asthma-associated genes, they learned that as interferon gamma levels rose, the levels of a protein called secretory leukocyte protease inhibitor (SLPI) dropped.

In follow-up experiments, the team found that boosting SLPI levels reduced airway hyper-reactivity in the animal model.

"We'd like to better understand why severe asthma occurs in most people right from the start," Dr. Anuradha Ray said. "We also want to find agents that can raise SLPI levels for clinical use."

In a new project that began this month, Drs. Anuradha Ray and Wenzel were recently awarded a five-year, $8 million grant from the National Institute of Allergy and Infectious Diseases (NIAID), also part of the National Institutes of Health (NIH), to continue studying the immune response and genetic roots of severe asthma in 120 patients and in animal models.

The research effort signifies a union of Pitt and UPMC scientists, immunologists and clinicians working under the NIAID grant to bring bench to bedside and bedside to bench, Dr. Wenzel said.

"It's the unmet need of asthma," Dr. Wenzel said. "This is one of the first true opportunities to integrate top-tier immunologists with translational clinical science. To find the many different mechanisms involved, you need a team effort such as this one."

Provided by University of Pittsburgh Schools of the Health Sciences

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