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A century-old puzzle comes together: Scientists ID potential protein trigger in lung disease sarcoidosis

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Lung researchers at Johns Hopkins have identified a possible protein trigger responsible for sarcoidosis, a potentially fatal inflammatory disease marked by tiny clumps of inflammatory cells that each year leave deep, grainy scars on the lungs, lymph nodes, skin and almost all major organs in hundreds of thousands of Americans.

The disorder, whose cause has been a persistent mystery for nearly a century, strikes mostly young adults and disproportionately affects African Americans.

The link between sarcoidosis and overproduction of the suspected protein trigger, called serum amyloid A, was revealed after a six-year investigation encompassing more than two dozen laboratory experiments, including some on diseased lung tissue samples from 86 patients in the Baltimore area.

"The increase in production of serum amyloid A explains for the first time how inflammation can persist in the lungs without being triggered by an active infection," says study senior investigator and pulmonologist David Moller, M.D., a professor at the Johns Hopkins University School of Medicine. Moller is also director of the sarcoidosis clinic at The Johns Hopkins Hospital.

Study lead investigator Edward Chen, M.D., says the new findings also

clear the path for developing drug treatments or vaccines that can block serum amyloid A from binding to cell receptors and kicking off inflammation.

In the short term, however, Moller says his team has plans to use the study results to create diagnostic tests that could better predict which people with the disease are likely to heal on their own or are more likely to suffer persistent inflammation, which can lead to scarring, difficulty breathing, and heart failure that can only be fixed by lung transplantation .

In a report published in February in the American Journal of Respiratory and Critical Care Medicine, the Johns Hopkins scientists described their research on what was behind the microscopic clusters of inflamed tissue and white blood cells, or granulomas, which are a defining feature of sarcoidosis.

Such lung lesions are not unique to sarcoidosis and can be triggered by infections, such as in tuberculosis, which is often confused with sarcoidosis. But unlike tuberculosis, sarcoidosis is not an infectious disease, does not yield to antibiotics, and is not limited to any particular organ, occurring as well in the eyes, skin, brain, heart and liver.

Of particular interest to researchers was the role played by so-called amyloids, a set of proteins known to cause other persistent inflammatory conditions, such as amyloidosis. Indeed, a different kind of amyloid has been tied to plaques in the brain tissue of people with Alzheimer's disease.

Key among the researchers' findings in sarcoidosis patients was that serum amyloid A stood out because it was heavily concentrated within the granulomas in diseased and scarred lung tissue. Researchers found the protein a hundred to a thousand times more widespread in

sarcoidosis tissue samples than in samples from people with tuberculosis, another granuloma-forming lung disease. Similarly elevated amyloid levels were seen in comparison tests with tissue samples from people with lung cancer and Crohn's disease.

Further tests in patients' lung cell cultures showed that adding serum amyloid A spiked production of at least a half-dozen key inflammatory chemicals known to be involved in damaging tissue.

In another series of experiments in mice, the team discovered that granuloma formation in the lungs sped up when the mice were given injections of synthetic serum amyloid A. Mice had previously been injected with specially coated plastic beads designed to trigger sarcoidosis-like lesions. Adding the synthetic protein led to the same biochemical reactions in the mice as observed in humans, suggesting to the researchers that serum amyloid A played a key role in triggering sarcoidosis.

To better understand how serum amyloid A might be driving granuloma formation, the team used special antibodies to block various cell surface receptor sites where the protein would bind to the white blood cells and spur inflammation. Tests in human lung cells showed that blocking one particular receptor, toll-like receptor-2 (TLR2), inhibited the sustained inflammatory reaction typically associated with sarcoidosis. But when left to bind on its own, without an antibody blocking TLR2, the open receptor could attach to serum amyloid A, and raised production of inflammatory chemicals would ensue.

"Not only have we shown that serum amyloid A is a key protein trigger in sarcoidosis, but we also have evidence that the resulting inflammation is dependent on binding the protein at toll-like receptor-2, which opens up a host of possibilities that drugs blocking this binding site could prove an effective treatment for this disease," says Chen, an assistant professor

at Johns Hopkins.

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