New biomarkers can help target treatment for chronic skin disease sarcoidosis

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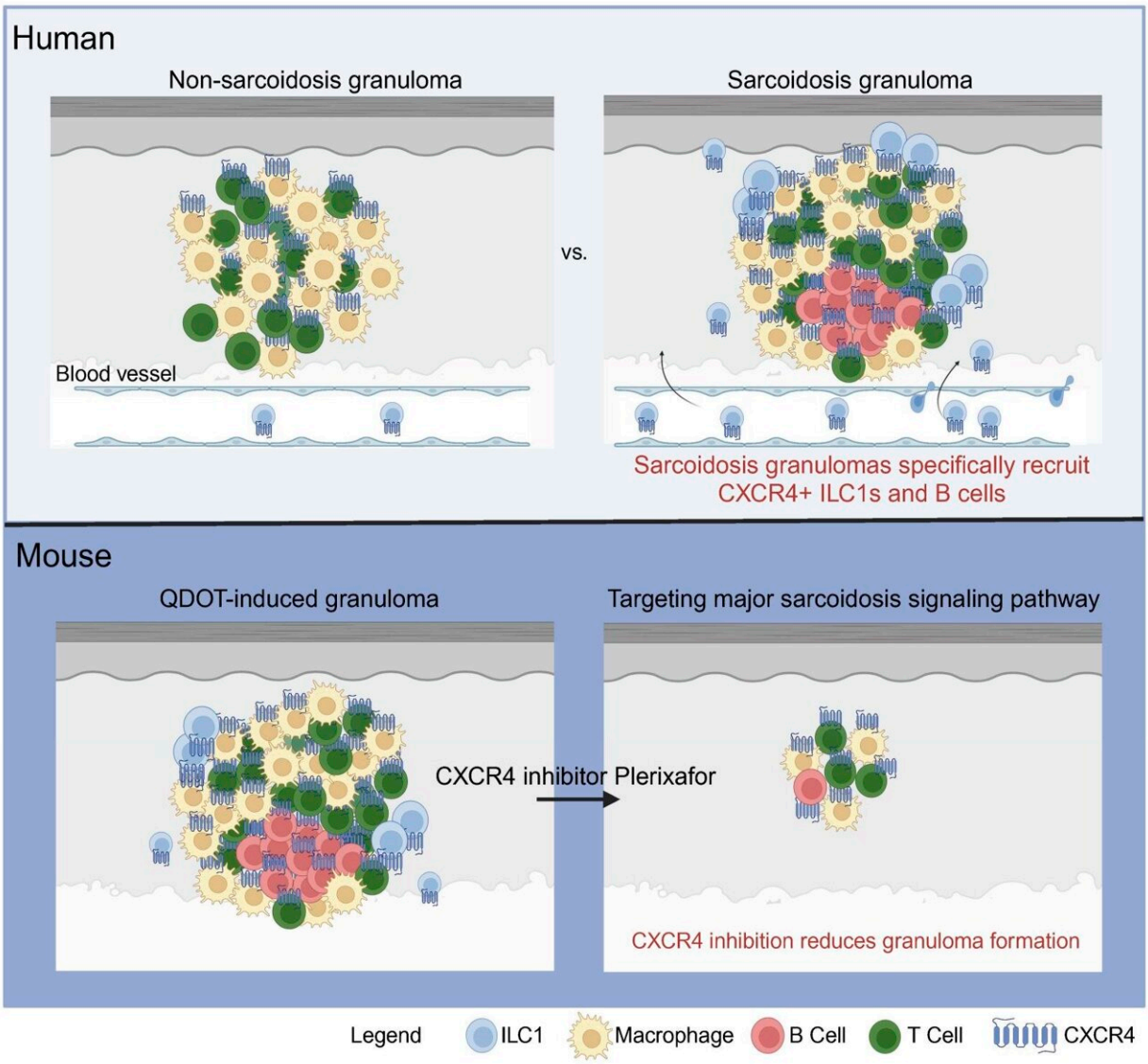

Credit: *Journal of Clinical Investigation* (2024). DOI: 10.1172/JCI178711

Sarcoidosis is a rare systemic disease that afflicts an estimated 200,000 people in the U.S., more often people who are Black and more women than men, particularly when it causes chronic skin disease. Now, clinicians may be better able to diagnose, monitor, and treat the condition, thanks to new research from scientists at the Perelman School of Medicine, published in the *Journal of Clinical Investigation*.

Using skin, lung, and blood samples from sarcoidosis patients and other patients with granulomas (lumps), the team found that cells called type 1 innate lymphoid cells (ILC1s) are found at much higher levels in the granulomas of patients with sarcoidosis.

They also found that targeting a pathway, called CXCR4, that is turned on in these cells can inhibit granulomas from forming. These findings suggest that clinicians may be able to diagnose sarcoidosis by measuring patients' ILC1 levels, and potentially even treat the condition by using already available medications that inhibit the CXCR4 pathway.

"Along with the challenge of diagnosing sarcoidosis, up to this point, first-line therapy for sarcoidosis patients is broad immunosuppression with steroids, which is like using a blunt instrument to make a fix," said Thomas Leung, MD, Ph.D., an assistant professor of Dermatology at Penn.

"By identifying a cause of the disease, we may have found a better way to diagnose the disease as well as a potential treatment that avoids major side effects."

Sarcoidosis is characterized by the formation of granulomas, or clumps of immune cells, in organs, including the skin. The granulomas in the skin can form large lumps and often occur on the face. These lesions can

compromise breathing and can severely affect patients' interpersonal interactions and quality of life.

Importantly, granulomas can also form internally, in and around vital organs like the heart, lungs, and eyes, causing chronic inflammation and permanent organ scarring, sometimes leading to death.

Diagnosing sarcoidosis still poses immense challenges for clinicians since there is no single test to confirm sarcoidosis, said study co-author Misha Rosenbach, MD, the Paul R. Gross Professor of Dermatology and the director of Penn's Cutaneous Sarcoidosis & Granulomatous Disease Clinic.

"Knowing that type 1 innate lymphoid cells are a biomarker for sarcoidosis should lead to timelier diagnoses for patients," said Rosenbach.

The researchers began by comparing samples of affected and unaffected skin in sarcoidosis patients to samples from patients with skin granulomas caused by other unrelated diseases. The levels of ILC1 were specifically higher in sarcoidosis skin tissues. This held true when the researchers looked at lung granulomas from sarcoidosis.

But what really keyed researchers into ILC1 as a culprit was the 12-fold increase in ILC1 circulating in the blood of patients with sarcoidosis, levels of which seemed to change when patients were treated.

"ILC1 is an important part of the body's inflammatory response," said Leung. "Like everything, however, when it comes to the human body, the right balance is always critical, and a 12-fold difference between patients with sarcoidosis and patients without the disease is substantial and made us suspicious of these cells."

The study authors then developed a mouse model to explore granuloma biology and found that ILC1 cells were necessary for granulomas to form. That led to the investigators' final tests into whether controlling ILC1s and the related inflammatory pathway CXCR4 within mice with sarcoidosis could prevent the formation of granulomas. Both approaches led to fewer granulomas forming compared to controls.

"We found that CXCR4 signaling is crucial to the development of tissue granulomas, and blocking that signal can inhibit granuloma formation," said Leung. "CXCR4 inhibitors are already available in the clinic as an injection and used to safely mobilize stem cells before stem cell transplants.

"I'm eager to work with Misha Rosenbach and the sarcoidosis clinic at Penn to run a clinical test to study whether repurposing these medications may be the first targeted treatment for sarcoidosis. Repurposing medications is more efficient than developing a new drug because the safety and nuances of the drug are already well known."

George Cotsarelis, MD, the chair of the Department of Dermatology and the Milton Bixler Hartzell Professor of Dermatology at Penn, underscored that dermatology is playing a key role in this type of research.

"We have said for decades that the skin is a 'window' into the body," he said. "Studying the skin is an efficient way to investigate systemic, multiorgan diseases."

More information: Satish Sati et al, Recruitment of CXCR4+ type 1 innate lymphoid cells distinguishes sarcoidosis from other skin granulomatous diseases, *Journal of Clinical Investigation* (2024). DOI: 10.1172/JCI178711

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