

Research uncovers connections between psoriasis and joint disease

June 8 2020



Nicole Ward, professor of nutrition and dermatology at the Case Western Reserve University School of Medicine. Credit: Case Western Reserve University

A team led by Case Western Reserve University School of Medicine researchers has made two major discoveries involving psoriasis, a chronic and debilitating skin disease with no known cure.

The researchers found that an overabundance of a protein known as KLK6 can produce and worsen the [skin inflammation](#) characteristic of psoriasis, and—even more significant—that KLK6 can play a key role in damaging the joints and bones of people with the disorder.

The research also revealed that normalizing the level of KLK6 can eliminate [skin inflammation](#) and lessen the arthritis-like damage. The research, which used mouse models and patient skin samples, appeared this spring in *The Journal of Clinical Investigation*.

While scientists had known that about a third of people diagnosed with psoriasis also develop psoriatic arthritis (PsA), the reason wasn't clear.

"To discover that turning down KLK6 eliminated the skin inflammation and even improved the arthritis-like changes—that was unbelievable," said Nicole Ward, the study's principal investigator and a professor of nutrition and dermatology at the medical school. "This suggests that clinicians need to aggressively treat patients with psoriasis to prevent the arthritis changes, which generally occur after the skin disease presents itself. Since the joint and bone damage are largely irreversible in patients, prevention becomes critical."

Study co-authors included an interdisciplinary team of 20 researchers from Cleveland Clinic Lerner Research Institute, the University of Michigan and New York University.

Psoriasis is characterized by red, scaly patches that are itchy and painful; it is chronic, incurable and affects 2% to 3% of the population worldwide. The associated psoriatic arthritis can cause disabling damage to bones and joints. Because that damage also is irreversible, study researchers said it is critical to identify patients with psoriatic arthritis early to prevent further destruction to their bones, tendons and joints.

The study is the latest in a series Ward and her colleagues have conducted involving psoriasis and Kallikrein-related peptidase 6, or KLK6.

They undertook the current research to understand how the cellular and molecular mechanisms of KLK6 and another protein, known as protease-activated receptors (PAR)1, promote skin inflammation. Ward said that until now, little was known about the connections between KLK6 and psoriasis or psoriatic arthritis, and even less was known about PAR1 and psoriasis.

KLK6 controls reactions within—and sometimes even outside—cells. Increasing [scientific evidence](#) suggests it also may have a role in certain inflammatory skin diseases as well as cancer, multiple sclerosis and Parkinson's and Alzheimer's diseases.

PAR1 is a receptor protein, meaning it receives chemical signals from outside a cell, such as from KLK6. When such signals activate the receptor, they cause cellular/tissue responses, including inflammation.

Previously, Ward and colleagues found the skin of psoriasis patients contained as much as six times more KLK6 than normal. They also found that the PAR1 receptor was overproduced in skin and immune cells. Based on that, they theorized that KLK6 might drive inflammation by signaling through PAR1.

To address the latest question, genetic engineering was used to overproduce KLK6, which resulted in the development of a psoriasis-like [skin disease](#) as well as bone and joint disease. They also found that "knocking out," or deleting, PAR1 led to a reduction in skin inflammation and, "more profoundly," Ward said, a significant improvement in bone and joint problems. "These findings suggest that [chronic inflammation](#) originating in the skin has the capacity to cause

distant joint and bone destruction seen in arthritis."

The researchers then took psoriasis skin from patients, treated it with an FDA-approved PAR1 antagonist in a petri dish and showed significant decreases in several psoriasis markers.

Next, the researchers aim to study how skin inflammation causes arthritis-like damage and translate those findings to benefit patients. They also plan to study and compare models that do and don't develop [arthritis](#) to identify biomarkers that can predict the development of [psoriatic arthritis](#).

"If successful, this would be paradigm-shifting and would lead to a more personalized method for identifying which [psoriasis](#) patient will go on to develop PsA so we can modify their treatment accordingly," Ward said.

More information: Allison C. Billi et al, KLK6 expression in skin induces PAR1-mediated psoriasiform dermatitis and inflammatory joint disease, *Journal of Clinical Investigation* (2020). [DOI: 10.1172/JCI133159](#)

Provided by Case Western Reserve University

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