# Study finds healthy-appearing lupus skin predisposed to flares, rashes

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A graphic depicting a person with lupus. Credit: Justine Ross, Michigan Medicine.

People with lupus have overactive immune systems that attack their own tissue, causing inflammation throughout the body.

Around 70-80% of them will develop skin disease as part of their condition. And while it's thought that exposure to ultraviolet light

triggers the rashes, scientists are not sure how it ties together with the systemic inflammation.

A Michigan Medicine study now brings more clarity, as researchers found that the normal-appearing skin of lupus patients contains the same inflammatory signals that are detected when the skin develops a rash—sometimes at even higher levels. The results are published in *Science Translational Medicine*.

"This really starts to piece the puzzle together of how inflammation seen in lupus patients may be related to skin exposures such as UV light," said J. Michelle Kahlenberg, M.D., Ph.D., senior author of the study and rheumatologist at University of Michigan Health. "We were able to see the properties of normal-appearing skin in unparalleled resolution, suggesting that the skin is primed for inflammatory reactions."

The team of researchers used single-cell RNA-sequencing analysis to assess the biopsies of both normal-appearing skin and skin from rashes of seven lupus patients. The results reveal that elevated signals of interferon, a protein known to contribute to UV sensitivity, were robustly present in all lupus biopsies compared to healthy control skin—with the strongest signal coming from the healthy-appearing skin, not the inflamed skin.

These interferon-rich inflammatory properties weren't just found in the keratinocytes, the cells that make up the epidermis of the skin. Researchers saw the same inflammatory changes in the fibroblasts that generate the connective tissue of the skin.

"This is really important because we have a new drug that can block interferon signaling in lupus, and people are trying to figure out how best to use that medication," said Kahlenberg, who is also an associate professor of rheumatology at U-M Medical School. "So, validating this

abnormality in the interferon pathway could be essential for determining the best course of treatment for scores of lupus patients."

## Cell education

The researchers also took blood samples of the same patients to examine how immune cells are promoting skin inflammation in lupus. Their data suggest that a subtype of monocytes, important members of the innate immune system, are exiting the blood into the skin of lupus patients. Upon moving into the skin, they undergo a striking inflammatory transformation.

Kahlenberg calls it "cell education." The lupus skin environment itself—specifically, the interferon within the skin—appears to change the monocytes in a way that sets up the rest of the immune system to be turned on.

Interferon plays a critical role in the innate immune system. It alerts the cells to dangerous invaders such as viruses. In many autoimmune diseases, however, interferon is overproduced in the absence of any real threat, changing how immune cells behave.

"These interferon-educated immune cells seem to be priming many different cell types in the skin to overreact to stimuli with excessive inflammatory responses, manifesting as disfiguring skin lesions," said Allison C. Billi, M.D., Ph.D., co-first author of the study, dermatologist at U-M Health and assistant professor of dermatology at U-M Medical School. "We don't yet know all of the stimuli that can tip the balance and precipitate these rashes, but UV light certainly appears to be one of them."

Previous research analyzing the blood of lupus patients has struggled to identify potential biomarkers for disease flares. Knowing that the

monocytes became more inflammatory when traveling to the skin, Kahlenberg believes the same process could also trigger systemic immune flares in other organs affected by lupus, such as the kidney and brain.

"In future studies, we will want to look at these target organs to really understand what's going on," she said. "These cells transformed so robustly when they migrated into the skin it suggests that if we look for biomarkers only in the blood, we will likely miss what is really happening in the organs."

Billi says understanding changes at a cellular level will enable precision medicine in lupus patients, which would employ individualized analysis to guide medical decisions and treatment options.

"Research has been hampered by how differently lupus presents across individuals," she said. "By focusing on patients with lupus affecting a single organ—the skin—we have gained some insight into which cells are orchestrating lupus inflammation and how."

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