

Skin's immune 'alarm' may explain light-induced rashes in lupus patients

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Human skin structure. Credit: Wikipedia

Imagine being so sensitive to the sun's rays that you're forced to either slather yourself in sunscreen or risk a rash so severe it could leave permanent scars.

This is the unfortunate reality of many people with lupus. Up to 60 percent of patients with the autoimmune disease has some degree of sensitivity to ultraviolet light—a condition called photosensitivity. It can result in [skin](#) inflammation or a flare-up of a wide-range of [lupus symptoms](#), such as joint pain and fatigue.

For some patients, even the light of a photocopier is enough to trigger the disease's characteristic angry red rash.

"Studies on the photosensitivity aspect of lupus have shown a huge correlation between how photosensitive someone is and their quality of life," says J. Michelle Kahlenberg, M.D., Ph.D., assistant professor of internal medicine in the division of rheumatology at Michigan Medicine.

She and a multidisciplinary team of researchers are attempting to unlock the mystery behind this reaction. Their findings are published in the online version of *Annals of Rheumatic Diseases*.

Their work builds on a decade's worth of research examining the link between proteins called interferons and lupus itself. Interferons are released by cells in response to an invasion. Typically triggered by viruses, they also can be activated by bacteria and other external threats.

Interferons alarm other cells to bolster their defenses. The function is present in all people.

"Interferons are notoriously hard to measure but we've known they are elevated in most [lupus patients](#)," Kahlenberg notes. "In this experiment, we set out to see which ones were in the skin."

Gene editing offers insight

When they compared skin cells from patients with lupus and people with healthy skin, lupus epidermal skin cells called keratinocytes—the keratin-producing cells that make up the very top layer of skin—showed a significant increase in interferon kappa (IFN- κ).

Next, they generated keratinocytes without IFN- κ using CRISPR/Cas9 technology, which functions like a pair of genetic scissors, to remove the gene encoding the interferon. They then compared these skin cells to another set designed to overexpress IFN- κ .

"We found out that all type I IFN signaling goes down in basal keratinocytes when you delete, or knock out, the IFNK gene using CRISPR/Cas9; we also observed that IFNK knock out keratinocytes are unaffected by UV light," says Mrinal Sarkar, Ph.D., a research investigator with the department of dermatology at U-M.

Conversely, [cells](#) overexpressing IFN- γ died when exposed to UV light.

"We think that the probable main function of IFN- γ in normal healthy skin is to fight off viral infections, such as HPV. But in lupus, this whole system is out-of-sync and overactive," explains Johann Gudjonsson, M.D., Ph.D., associate professor of dermatology.

Research moving forward

Even without exposure to UV light, lupus skin had higher baseline levels of IFN- γ . The overabundance of IFN- γ in lupus skin appears to amplify the inflammatory response and cell death.

The team is currently trying to uncover why IFN- γ is elevated in the skin of patients with lupus and how it regulates death in keratinocytes. They also wonder if there are similar mechanisms at play in other diseases with photosensitivity as a feature, such as dermatomyositis.

What makes this discovery particularly exciting, the team notes, is the fact that there are recently FDA-approved drugs, currently prescribed for rheumatoid arthritis, that can block interferons.

Using a drug called baricitinib, the U-M researchers were able to block [interferon](#) signaling and make lupus [skin cells](#) look like those in normal healthy skin. Baricitinib is currently in drug trials for [lupus](#), but not for photosensitivity.

"I'm excited to see this go from bench to bedside," says Kahlenberg. "It may actually happen that some of our work helps to push this forward."

More information: Mrinal K Sarkar et al, Photosensitivity and type I IFN responses in cutaneous lupus are driven by epidermal-derived interferon kappa, *Annals of the Rheumatic Diseases* (2018). [DOI: 10.1136/annrheumdis-2018-213197](#)

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