

Transcript Details

This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: <https://reachmd.com/programs/living-rheum/the-complexities-behind-lupus-understanding-its-multifactorial-mechanisms/32787/>

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The Complexities Behind Lupus: Understanding its Multifactorial Mechanisms

Announcer:

You're listening to *Living Rheum* on ReachMD. On this episode, Dr. Michelle Kahlenberg will discuss the underlying mechanisms behind lupus. Dr. Kahlenberg is a Professor of Internal Medicine and Dermatology as well as the Giles Boles and Dorothy Mulkey Research Professor of Rheumatology at the University of Michigan. Dr. Kahlenberg also spoke on this topic at the 2025 Congress of Clinical Rheumatology East conference. Let's hear from her now.

Dr. Kahlenberg:

To drill down to what do we think—at least, as far as we know right now—what the initiating mechanisms of lupus are, it's multi-layered. We know that there are genetic predispositions that run in families that increase the risk of people developing lupus, but it's not one to one.

Most people who get lupus have some genetic underlying risk. And then we think it's an interplay between the environment and repetitive immune activation cycles. By that, I mean we know that the innate immune system, which is our fast-responding type of immune system that makes a lot of inflammation to infection, environmental exposures, and things like UV light stimulation, that produces a lot of cytokines that activate our immune system. And in people who develop lupus, we think one of the very earliest changes that can happen is that they start to skew how much interferon they make as part of this cycle. And so interferons are a cytokine that we normally use to fight viruses, and in lupus patients, we know that even before lupus develops, you can see high levels of interferons present. And we think that these interferons are important for changing the regulatory mechanisms of the immune system so that instead of responding to a bacteria or virus and then turning back off, you might overrespond to the bacteria or virus and keep your immune system turned on a little bit too long or a little bit too aggressively, and so it tends to get a little bit messy. Instead of being a nice, tidy, controlled activation of the immune system, it gets a little sloppy, and you can bring up and activate autoreactive B and T-cells that then, once those are turned on and activated, can become memory autoreactive B and T-cells that then create this immune response against your body. And with repetitive infections, environmental triggers, sunlight exposure, or other things, those cells can replicate and get bigger, and you start to make detectable autoantibodies in your bloodstream. Eventually, over time, as the cycle repeats over and over, you eventually get symptoms and present with all sorts of things, like fevers, joint pain, rashes, and kidney damage. Lupus is very special because it can affect basically every organ in the body, but we think that's the general mechanism of how lupus gets going.

In terms of epigenetics, this is also a very interesting area of study. We know there are certain things that are already pushing the skewing of immune activation in lupus patients, but we don't know yet how early that starts and what the triggers are for that epigenetic. Is it coming from when you're a fetus and because of your mother's exposures, you get your epigenetics set as you're developing as a fetus? Or whether these are environmental exposures that are occurring and changing epigenetic in populations that are replicating, so your immune cells are constantly turning over, so do you get these epigenetic changes over time? In the skin, same thing—does UV light change the epigenetics of the skin so that you become more sensitive to sun over time? We don't fully understand how epigenetics are playing a role, but we know that they do get altered. But whether that's one of the reasons for getting disease in the first place we don't know yet.

Announcer:

That was Dr. Michelle Kahlenberg discussing the pathophysiology of lupus. To access this and other episodes in our series, visit *Living Rheum* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!