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For Immediate Release

LJI scientists uncover key clues to how a viral infection can lead to arthritis-like disease

By studying Chikungunya virus, LJI scientists shed light on how immune responses to viral infections may lead to persistent symptoms of autoimmune disease

LA JOLLA, CA—Chikungunya virus (CHIKV) is a mosquito-borne pathogen that has been identified in more than 110 countries around the world. The virus typically causes flu-like symptoms, but it can also trigger chronic, severe joint pain in some people.

Researchers at La Jolla Institute for Immunology (LJI) are working to understand how a viral infection can cause persistent joint pain that closely resembles rheumatoid arthritis, an autoimmune disease.

In a new study, LJI scientists share a critical first look at how the body's T cells target CHIKV. Their research suggests CD4+ T cells step up to fight the virus—and cause chronic inflammation in the process. This discovery may help explain why some people infected with CHIKV develop severe joint pain.

“Autoimmune diseases like rheumatoid arthritis have exactly these parameters," says LJI Assistant Professor Daniela Weiskopf, Ph.D., senior author of the new study and member of LJI's Center for Vaccine Innovation.

The findings, published recently in *Cell Reports Medicine*, offer new clues to why some viral infections appear to trigger autoimmune disease. The research may also help guide the development of therapies to block harmful inflammation.

Testing immune cells vs. Chikungunya virus

Weiskopf and her colleagues studied immune cells found in blood samples from a group of CHIKV patients in Colombia. The researchers tested how immune cells from these patients responded to small molecular chains, called peptides, from Chikungunya virus.

This experiment revealed which types of immune cells take the lead in fighting CHIKV infection. The researchers also captured the first-ever look at which sites on CHIKV, called viral epitopes, drew the strongest immune cell responses.

To their surprise, the researchers found that a type of T cells called CD4+ T cells showed a strong response to CHIKV. Although CD4+ T cells are a normal part of the body's anti-viral response, they are almost always accompanied by CD8+ T cells. Scientists have even nicknamed CD8+ T cells "killer" T cells because they play a very active role in fighting infections.

Yet the new study shows that CD4+ T cells are most active in fighting CHIKV virus. These same CD4+ T cells stay in the body as "memory" T cells after the infection is gone.

The researchers found that 87 percent of patients had detectable levels of CHIKV-specific memory CD4+ T cells in their blood six years after their initial infection. In contrast, only 13 percent of patients still had CHIKV-specific memory CD8+ T cells in their blood after six years.

According to Weiskopf, this kind of CD4+ T cell profile is more commonly seen in patients with autoimmune diseases. “I’m an infectious disease researcher, but I could see that this T-cell response looked awfully like what we see in autoimmune disease,” says Weiskopf.

Not your typical T cells

This CD4+ T cell activity may help explain the association between CHIKV infection and chronic, autoimmune-like disease.

"There are many studies in mice showing that CD4+ T cells are pathogenic," adds study co-first author Rimjhim Agarwal, a UC San Diego Graduate Student and member of the Weiskopf Lab. "So we needed to know what CD4+ T cells are doing in people with CHIKV."

The researchers took a closer look exactly how CD4+ T cells fought CHIKV infection. Normally, CD4+ T cells are "polyfunctional," meaning the cells can churn out many kinds of signalling molecules to help coordinate the body's immune response to a pathogen.

But CHIKV patients who developed severe joint pain had more "monofunctional" CD4+ T cells. Even years after initial infection, their T cells primarily produced an inflammatory molecule called TNF-alpha. This molecule helps direct immune cell activity during an infection, but TNF-alpha is not supposed to linger long after a virus has been cleared.

The new study offers evidence that these monofunctional CD4+ T cells may be the culprits behind joint pain and chronic inflammation following CHIKV infection. Although there's still a lot to learn, the researchers say future therapies that inhibit TNF-alpha may hold promise for treating arthritis-like symptoms in CHIKV patients.

Next steps for helping patients

The new study raises many big questions. Agarwal is currently working to explain a strange phenomenon—why are women in their forties much more likely to develop chronic joint pain following CHIKV infection?

Last year, Agarwal won funding through LJI's Tullie and Rickey Families SPARK Awards for Innovations in Immunology to investigate this sex-based difference. Her SPARK project, specifically funded by the Rosemary Kraemer Raitt Foundation Trust, may help shed light on whether CD4+ T cells are mistakenly attacking the body's own tissues when responding to CHIKV.

This work comes as more scientists today look at possible connections between viral infections and autoimmune disease. Other viruses, such as the mosquito-borne dengue virus, can also cause severe, chronic joint pain. Many people today are also dealing with "long COVID," chronic and debilitating autoimmune-like inflammation that often follows SARS-CoV-2 infection.

"More and more people are realizing, particularly after seeing the long-term effects of SARS-CoV-2, that viral infection can trigger autoimmune-like disease," says Agarwal. "We still have a lot more questions than answers right now, but we want to understand the relationship between viruses and autoimmune diseases."

Additional authors of the study, "Chikungunya virus-specific CD4+ T cells are associated with chronic chikungunya viral arthritic disease in humans," were James Chang, Fernanda H Côrtes, Calvin Ha, John Villalpando, Izabella N. Castillo, Rosa Isela Gálvez, Alba Grifoni, Alessandro Sette , Claudia M. Romero Vivas, Mark T Heise, Lakshmanane Premkumar, and Andrew K Falconar.

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Learn more:

Immune Matters Magazine article: For some women, one mosquito bite leads to chronic pain

About La Jolla Institute

La Jolla Institute for Immunology (LJI) is dedicated to understanding the intricacies and power of the immune system so that we may apply that knowledge to promote human health and prevent a wide range of diseases. Since its founding in 1988 as an independent, nonprofit research organization, the Institute has made numerous advances leading toward its goal: life without disease. Visit lji.org for more information.

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