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Discovery shows fat triggers rheumatoid arthritis

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Scientists have discovered that fat cells in the knee secrete a protein linked to arthritis, a finding that paves the way for new gene therapies that could offer relief and mobility to millions worldwide.

"We found that fat in the knee joints secretes a protein called pro-factor D which gives rise to another protein known as factor D that is linked to arthritis," said Nirmal Banda, Ph.D., associate professor of medicine in the Division of Rheumatology at the University of Colorado School of Medicine. "Without factor D, mice cannot get rheumatoid arthritis."

Rheumatoid arthritis is an autoimmune condition that gradually destroy bones, muscles, joints, cartilage and other connective tissue. Over 1% or about 1.3 million Americans suffer from it.

Banda, senior author of the study published this week in the *Journal of Immunology*, has spent the last 14 years tracking down the causes of rheumatoid arthritis in collaboration with CU School of Medicine professors Michael Holers, MD, and William Arend, MD.

Now, with the discovery of pro-factor D in mice with rheumatoid arthritis, he is working on gene therapies to eliminate the protein in localized areas. However, these findings still need to be extended to humans.

"We are looking at vaccines, drugs or inhibitors to stop the local secretion of pro-factor D in the mouse," he said. "Our goal would be to

stop the disease before it progresses and leads to joint destruction."

Factor D is part of the complement system, a complex array of over 40 proteins that help the body fight off bacteria and other pathogens. In studies with arthritic mice, Banda previously found that the complement pathway involving factor D made the mice susceptible to inflammatory arthritis.

In his latest study, he discovered that removing factor D, rather than the entire complement system, achieves the same result without compromising other parts of the system that can fight infection.

"We know that fat is normally present around all organs of the body," he said. "But what we didn't know until now was that the fat is secreting this protein which actually triggers arthritis in the joints."

He noted that fat does the same thing in all the joints, not just the knees. That means new medications resulting from this discovery could treat inflammatory arthritis throughout the body.

While it's theoretically possible to destroy the entire complement system in humans to prevent arthritis, it eventually returns along with a renewed risk of contracting the disease. In the meantime, patients can get infections and other complications because they lack this critical part of the immune system.

"The complement system is both friend and foe," Banda said. "We believe we can shut down one part of the complement system that triggers disease without shutting down the rest. If so, we will be making a major stride toward treating and perhaps even curing rheumatoid arthritis."

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