

# Regulatory immune cell diversity tempers autoimmunity in rheumatoid arthritis

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Untangling the root cause of rheumatoid arthritis has been a difficult task for immunologists, as decades of research has pointed to multiple culprits in our immune system, with contradictory lines of evidence. Now, researchers at The Wistar Institute announce that it takes a diverse array of regulatory T cells (a specialized subset of white blood cells) to prevent the immune system from generating the tissue-specific inflammation that is a hallmark of the disease. Regulatory T cell diversity, the researchers say, provides a cumulative protective effect against rheumatoid arthritis. When that diversity is not present, it allows the immune system to attack joints.

The Wistar scientists presented their findings, developed in a [mouse model](#) of [rheumatoid arthritis](#), in the May 1 issue of the [Journal of Immunology](#). Defining the immune mechanisms involved in rheumatoid arthritis could point to new therapies for the disease.

"Our results show, surprisingly, that suppressing the immune response against a single target will not shut down the inflammatory response that causes rheumatoid arthritis," said Andrew J. Caton, Ph.D., senior author and professor in The Wistar Institute Cancer Center's [Tumor Microenvironment](#) and Metastasis program. "Instead, an array of inflammation-stimulating [antigens](#) may be involved in causing the disease, since our study shows that an array of regulatory T cells is required to temper the immune system's attack on joints."

Rheumatoid arthritis (RA) is an autoimmune disorder that occurs as the

[immune system](#) attacks the synovium, the membrane that lines all the joints of the body. It is a common disorder that causes uncontrolled inflammation—resulting in pain and swelling—around the joints. It is thought that approximately one percent of the adult population, worldwide, suffers from rheumatoid arthritis. RA has shown to be exacerbated by drinking and smoking, and the disease can lead to an overall increased risk of death.

While the exact cause of RA is unknown, the Caton laboratory and others have shown that a variety of [white blood cells](#) called [regulatory T cells](#) (or Tregs) are a necessary component to either restrain (or encourage) the immune system's [inflammatory response](#). Tregs are activated as molecules on their surface membranes called T cell receptors interact with "friendly" or "self" molecules—a way for the immune system to recognize friend from foe. Mismanagement of these Tregs, which normally serve to restrain the immune system from over-reacting to healthy tissue, could then lead to runaway inflammation.

In this study, the researchers sought to examine how T cell receptors affect the ability of Tregs to suppress arthritis in a mouse that had been bred to express a "self" molecule that drives arthritis. They showed that an array of Tregs given to the mice effectively stops arthritis. Unexpectedly, however, Tregs that are specific for the surrogate "self" molecule do not prevent arthritis.

"We find that the Treg responsible for recognition of the disease-initiating self antigen are sufficient for stopping arthritis, but a diverse repertoire of Tregs are very effective," Caton said. "All of these Tregs, together, influence other components of the immune system which serves to slow down the inflammatory process that causes RA."

According to Caton, their findings also point to a possible answer of why the immune system targets the membranes that line joints. Tregs

influence other types of T cells to produce a substance known as IL-17, and these cells often travel through the body's lymphatic system where they then drain out into the joints.

"The big unanswered question of RA is 'why are joints targeted?'" Caton said. "Of all the tissues in the body, of all the places our immune system could attack, this question remains."

"One idea is that the immune system isn't deliberately attacking joints in patients with rheumatoid arthritis," Caton said, "but the joint inflammation is a side effect of the natural tendency of these cells to accumulate in these areas of the body."

Provided by The Wistar Institute

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