

Rheumatoid arthritis finding may lead to new inflammation blockers

November 22 2021, by Sara Tiner



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Mayo Clinic researchers have linked the T cell dysfunction seen in rheumatoid arthritis with a metabolic deficiency, reported in a new *Nature Immunology* publication.

In "helper" T cells from patients with rheumatoid arthritis, low levels of a specific amino acid lead to cellular miscommunication, but supplying it may provide a new therapeutic strategy for autoimmune disease.

Rheumatoid arthritis is an autoimmune disorder characterized by chronic inflammation, including high levels of a [cytokine](#) called tumor necrosis factor, or TNF. This protein is used to recruit immune system resources and can cause cell death (necrosis).

"For the last 25 years, tumor necrosis factor has been an important therapeutic target to treat autoimmune disease and tissue inflammation," says Cornelia Weyand, M.D., Ph.D., a Mayo Clinic immunologist and rheumatologist. "The introduction of tumor necrosis factor-inhibitors was a paradigm shift for the management of inflammatory disease. But while they block the action of TNF in the inflamed tissue site, they cannot prevent the production of the cytokine. Therefore, they cannot treat the root cause of TNF-induced disease." Dr. Weyand is senior author of the new publication.

Based on data collected over more than 20 years of work, Dr. Weyand's team began investigating helper T cells. They coordinate immune response, but they also can remain in the body after infection to help the immune system respond more quickly should the invader return. But it's not just previous encounters with pathogens that these cells remember.

"Unfortunately, these T cells can also memorize their own mistakes, and in patients with rheumatoid arthritis, they lead the attack against the joints," says Dr. Weyand.

Trailing T cell dysfunction to its source

In collaboration with Mayo Clinic patients, as well as their rheumatologists and surgical teams, researchers found that T cells are a significant source of tumor necrosis factor. They turned to cell and

mouse models to determine why and eventually discovered that the T cells had a defect in their [mitochondria](#).

"We made the observations that T cells from patients with rheumatoid arthritis have low-performing mitochondria, and by screening the cells for their mitochondrial products, we found that the rheumatoid arthritis T cells lack the amino acid aspartate," explains Dr. Weyand.

Through a series of experiments, the researchers discovered that aspartate acts as a messenger between the mitochondria and the [endoplasmic reticulum](#). When mitochondria decrease aspartate communication with the endoplasmic reticulum, that organelle assumes the mitochondria are under stress. The endoplasmic reticulum begins to expand and overproduce proteins in response, one of which is tumor [necrosis](#) factor.

"In essence, TNF hyperproduction is a result of a metabolic defect," explains Dr. Weyand. "Misnourished T cells dedicate themselves to TNF production and become highly efficient pro-inflammatory effector cells."

Treating autoimmune disease at the root

Equipped with this knowledge, Dr. Weyand hopes researchers will develop new therapeutic strategies to combat excess TNF.

"This will be of great importance for our patients because many become resistant to standard TNF blockers. Of equal importance is the recognition that metabolic defects within cells can lead to disease," says Dr. Weyand. "We want to develop strategies that can repair the mitochondrial defect, replenish the [aspartate](#) and successfully suppress tissue inflammation."

In addition to Dr. Weyand, other authors—all from Mayo Clinic—are Bowen Wu, Ph.D.; Tuantuan Zhao, Ph.D.; Ke Jin, Ph.D.; Zhaolan Hu, Ph.D.; Matthew Abdel, M.D.; Kenneth Warrington, M.D.; and Jörg Goronzy, M.D.

More information: Bowen Wu et al, Mitochondrial aspartate regulates TNF biogenesis and autoimmune tissue inflammation, *Nature Immunology* (2021). [DOI: 10.1038/s41590-021-01065-2](https://doi.org/10.1038/s41590-021-01065-2)

Provided by Mayo Clinic

Citation: Rheumatoid arthritis finding may lead to new inflammation blockers (2021, November 22) retrieved 25 April 2024 from <https://medicalxpress.com/news/2021-11-rheumatoid-arthritis-inflammation-blockers.html>

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