Scientists unearth potential new therapeutic target for inflammatory diseases such as lupus and sepsis

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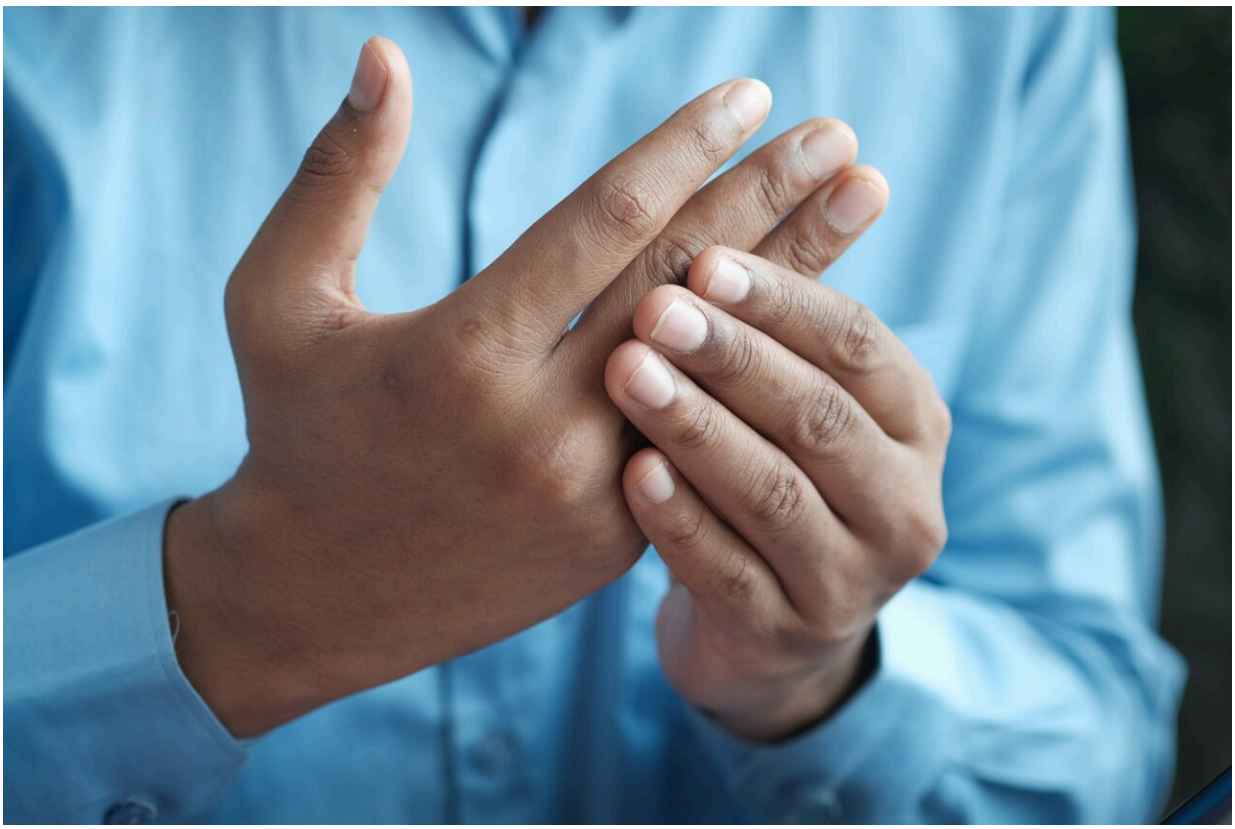

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Scientists working in the School of Biochemistry and Immunology in the Trinity Biomedical Sciences Institute at Trinity College Dublin have

made an important breakthrough in understanding what goes wrong in our bodies during the progression of inflammatory diseases and—in doing so—unearthed a potential new therapeutic target.

The scientists have found that an enzyme called fumarate hydratase is repressed in macrophages, a frontline inflammatory cell type implicated in a range of diseases including lupus, arthritis, sepsis and COVID-19.

Professor Luke O'Neill, Professor of Biochemistry at Trinity, is the lead author of the research article that has just been published in the journal, *Nature*. He said, "No one has made a link from fumarate hydratase to inflammatory macrophages before and we feel that this process might be targetable to treat debilitating diseases like lupus, which is a nasty autoimmune disease that damages several parts of the body including the skin, kidneys and joints."

Joint first-author Christian Peace added, "We have made an important link between fumarate hydratase and immune proteins called cytokines that mediate inflammatory diseases. We found that when fumarate hydratase is repressed, RNA is released from mitochondria which can bind to key proteins 'MDA5' and 'TLR7' and trigger the release of cytokines, thereby worsening inflammation. This process could potentially be targeted therapeutically."

Fumarate hydratase was shown to be repressed in a model of sepsis, an often-fatal systemic inflammatory condition that can happen during bacterial and viral infections. Similarly, in blood samples from patients with Lupus, fumarate hydratase was dramatically decreased.

"Restoring fumarate hydratase in these diseases or targeting MDA5 or TLR7 therefore presents an exciting prospect for badly needed new anti-inflammatory therapies," said Prof. O'Neill.

This newly published work is accompanied by another publication by a group led by Professor Christian Frezza, now at the University of Cologne, and Dr. Julien Prudent at the MRC Mitochondrial Biology Unit (MBU), who have made similar findings in the context of kidney cancer.

"Because the system can go wrong in certain types of cancer, the scope of any potential therapeutic target could be widened beyond inflammation," added Prof. O'Neill.

More information: Luke O'Neill, Macrophage fumarate hydratase restrains mtRNA-mediated interferon production, *Nature* (2023). DOI: 10.1038/s41586-023-05720-6.
www.nature.com/articles/s41586-023-05720-6

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