The discovery of a new regulator affecting immune cells could lead to new treatments to reduce inflammation in diseases including arthritis and severe COVID 19.
A large research collaboration, led by the University of Exeter's MRC Center for Medical Mycology, has focused on how immune cells sense their environment. This activity triggers responses which are finely balanced, to protect against disease and infection, and to reduce cell-damaging inflammation.

The research, titled "Recognition and control of Neutrophil Extracellular Trap formation by MICL" published in *Nature*, looked at the behavior of a receptor known as MICL, and its role in both preventing inflammation and protecting against infection.

Lead author Dr. Mariano Malamud, from the University of Exeter, said, "We've discovered that MICL is a key receptor that causes severe inflammatory disease when its functions are altered. This opens the door to the development of new therapies that target MICL, which could reduce the severity of inflammatory diseases and protect against infection."

Most receptors in the immune system sense their environment and send signals to cells, telling them to activate in response to changes such as infection or tissue damage. The team's work has revealed that MICL does the opposite, inhibiting the activation of the cell. This is an important function, as over-activation of cells can lead to cell damage and the development of auto-immune diseases if left unchecked.

The team went on to demonstrate the essential role that MICL plays in regulating inflammation in severe COVID 19, as well as arthritis and some other autoimmune diseases.

The new research, conducted in mice and verified in patients, focuses on the function of MICL present on the most abundant form of immune cell called a neutrophil.
As a result of an autoimmune disease or infection, neutrophils can undergo NETosis, a form of programmed cell death which is key for controlling infections but is very inflammatory. The team has found that MICL is able to detect this, and its inhibitory activity prevents more neutrophils from dying in this way.

NETosis cell death has been linked to several inflammatory diseases in humans, including Lupus, Rheumatoid arthritis and severe COVID. These inflammatory diseases lead to the production of antibodies that bind to MICL, preventing its inhibitory function and resulting in more severe disease.

Conversely, the study showed that increasing NETosis by blocking MICL function can protect against infection, such as those caused by fungi.

In mice with arthritis, the group showed that genetic loss of MICL led to more severe disease due to the excessive formation of NETs. More severe disease also occurred in normal mice when antibodies targeting MICL were applied.

Indeed, more severe disease was also seen in human arthritis patients who possessed antibodies targeting MICL, and the researchers could directly show that these patient antibodies drove exacerbated inflammatory response, using cell samples in labs.

Senior author Professor Gordon Brown, from the University of Exeter, said, "We've been working on how immune cells sense their environment for over 20 years, and this breakthrough is really exciting, revealing how the inhibition of inflammatory processes is finely balanced between controlling infection and the development of autoimmune disease"

More information: Gordon Brown, Recognition and control of
www.nature.com/articles/s41586-024-07820-3

Provided by University of Exeter

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