New Discovery: A Pathway That Can Completely Stop Inflammation in Rheumatoid Arthritis

Rheumatoid arthritis prevents the immune system from effectively using its "off switch" in the inflammatory process. Cytokines – the messenger proteins that carry action signals to cells – just can't seem to communicate "no". The cells that are supposed to halt inflammation don't. The cells promoting inflammation continue unstopped. Joints deteriorate, pain increases.

But now, for the first time, HSS scientists and rheumatologists have pinpointed what seems to be a key component of that crucial "no": the *immunoreceptor tyrosine-based activation motif coupled receptors* – the ITAM pathway. The researchers observed the ITAM pathway fully stopping the inflammatory process.

"It completely turns things off," reports HSS Associate Chief Scientific Officer Lionel Ivashkiv, MD, who led the multi-center study. "What we saw was the ITAM pathway triggering a complete inhibition of the inflammatory response."

At the outset, the team knew the ITAM pathway was involved in regulating inflammation. It had been shown to suppress so-called Toll-like receptors on pathways that promote inflammation. But no one knew exactly how. What's more, the ITAM pathway had never been established – or even studied – as specifically involved in rheumatoid arthritis.

"In the 20 years or so I have been studying regulation of inflammation, this seems to be the most potent inhibitory mechanism we have ever seen."

– Lionel Ivashkiv, MD,
Associate Chief Scientific Officer,
David H. Koch Chair in
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Next

Earlier research had also hinted a second pathway could be involved. Perhaps cytokines produced by the ITAM pathway signaled this not yet identified anti-inflammatory pathway to start doing its job and stop inflammation. The team thought they might be able to pinpoint which one.

Pathways Triggered, Inflammation Halted

What they found was a secondary pathway and more. (Specific findings in sidebar on right) Somehow the ITAM pathway can orchestrate a complete halt to inflammation.

Possibly the ITAM pathway helps integrate the extensive cross-talk that must necessarily happen among the cytokines of the many pathways involved in inflammation.

Discovering exactly how the ITAM pathway can so fully stop the inflammatory process will be the team's next focus.

As Dr. Ivashkiv notes, "This is a exciting area of rich promise. We've seen inflammation stopped. We know the ITAM pathway is responsible. Our goal is find out how and why. And then develop new treatments that can harness or control the ITAM pathway's natural ability to stop inflammation completely. Ultimately bringing freedom from pain to arthritis sufferers everywhere."

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Funded by grants from the National Institutes of Health, authors of the study include:

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Back to Top

Methods included:

- Using white blood cells similar to those found in rheumatoid arthritis: Activated the ITAM-associated receptors with fibrin(ogen) and immune complexes – proteins that are highly expressed at inflammatory sites

Findings included:

- Complete halt of the inflammatory process observed
- Implicating for the first time a negative role for calcium signaling downstream of ITAM-coupled receptors:
  Activation of the ITAM receptors set off a pathway known as *DAP12-Syk-Pyk2-p38-MSK* that was dependent on calcium signaling and discouraged pro-inflammatory cytokine production
- ITAM receptors also induced the anti-inflammatory cytokine IL-10 and proteins that have been implicated in suppressing cytokines: SOCS3, ABIN-3, A20, and Hes1
- Having seen in macrophages from patients with arthritis that the whole inhibitory pathway does not work, this study also suggests that crippling of beneficial pathways that usually serve to stop inflammation contributes to the unchecked inflammatory process in arthritis

Next steps:

- Elucidating molecular mechanisms of the ITAM pathway's ability to halt inflammation and further testing of its importance in arthritis and animal models of disease