

# Newly discovered signaling pathway could impact a variety of autoinflammatory diseases

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Researchers from Virginia Commonwealth University (VCU) Massey Cancer Center have discovered a new signaling pathway in sterile inflammation that could impact the treatment of diseases such as cancer, multiple sclerosis and rheumatoid arthritis. Their findings offer insight into the role that activation of interferon-regulatory factor 1 (IRF1), a protein that functions as a transcriptional activator of a variety of target genes, plays in the production of chemokines and the recruitment of mononuclear cells to sites of sterile inflammation.

Although it has been shown that interleukin 1 (IL-1) induces the expression of IRF1, the biological importance of this was uncertain. In this study, recently published in the journal *Nature Immunology*, investigators Tomasz Kordula, Ph.D., and Sarah Spiegel, Ph.D., members of the Cancer Cell Signaling research program at Massey and professors in the Department of Biochemistry and Molecular Biology at the VCU School of Medicine, found a new signaling pathway that links IL-1 to IRF1 in sterile inflammation.

IL-1, a key regulator of sterile inflammation, governs immune and inflammatory responses and has an important role in autoinflammatory diseases. IL-1 signaling triggers a process called polyubiquitination. Polyubiquitination is important to a variety of cellular functions. While one form of polyubiquitination has been called the "kiss of death" because it targets proteins for degradation, another form known as

K63-linked polyubiquitination is important to [cell signaling](#).

"For the first time, we found that K63-linked polyubiquitination is a mechanism of IRF1 activation," says Kordula. "Once activated, IRF1 induces potent chemokines that recruit immune cells to sites of sterile inflammation and promote healing."

Kordula and Spiegel, Mann T. and Sara D. Lowry Professor of Oncology and co-leader of the Cancer Cell Signaling research program at Massey and chair of the Department of Biochemistry and Molecular Biology at the VCU School of Medicine, previously discovered a link between chronic [inflammation](#) and cancer.

"As IRF1 affects the development of autoinflammatory diseases, targeting this previously unrecognized IL-1-induced cascade may be clinically important in the future," says Kordula. "Our next steps are to develop cell-specific, conditional IRF1 animal models in order to determine the cell type(s) responsible for the production of IRF1-mediated chemokines in the brain."

**More information:** [www.nature.com/ni/journal/vaop ...  
nt/full/ni.2810.html](http://www.nature.com/ni/journal/vaop...nt/full/ni.2810.html)

Provided by Virginia Commonwealth University

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