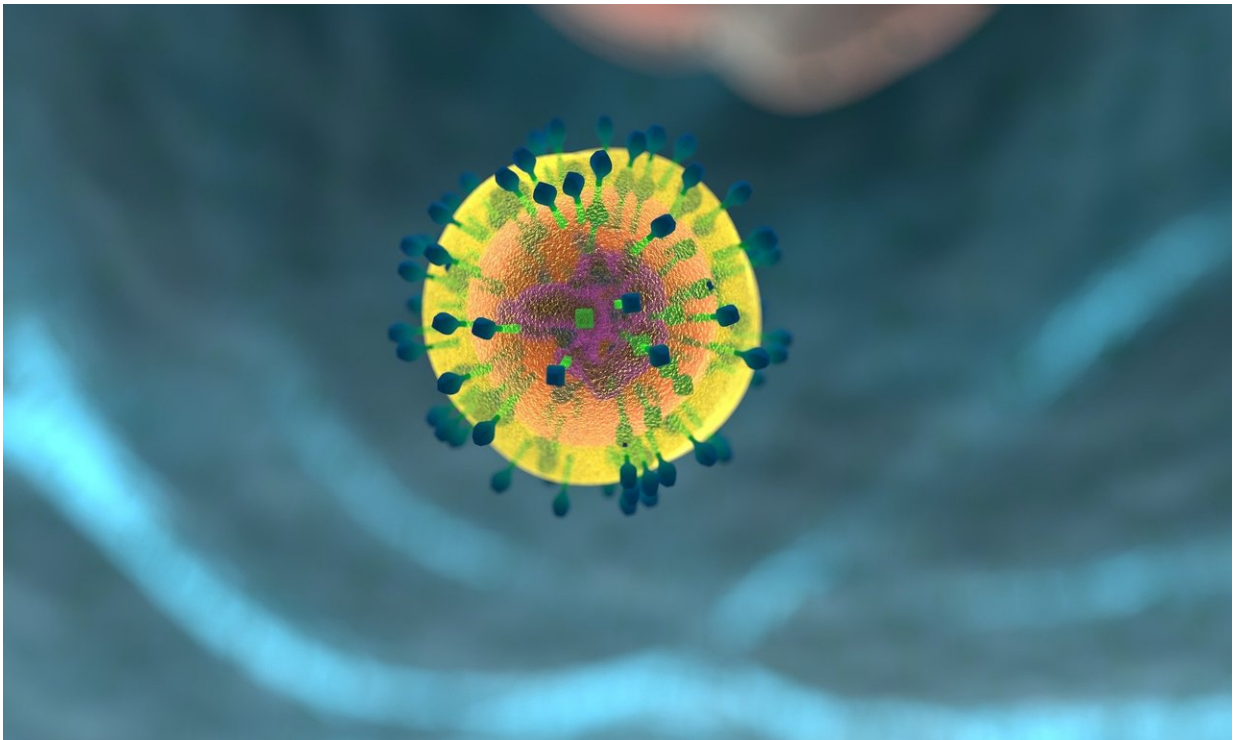


Phosphorylation of Regnase-1 lets IL-17 run amok

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When considering the role of the key immune molecule interleukin (IL)-17, the phrase "too much of a good thing" springs to mind. Because unlike some of its more sedate cytokine cousins which studiously direct the immune response to destroy invading pathogens, IL-17 can get a little carried away. So much so that excess inflammation caused by

IL-17 has been implicated in autoimmune disorders such as rheumatoid arthritis, psoriasis, and multiple sclerosis.

It is because of this destructive side of IL-17 that a research team led by Osaka University decided to examine exactly how mRNA-degrading protein Regnase-1 helps rein in the unruly cytokine. In an article published this month in the *Journal of Experimental Medicine*, the researchers describe how their results could provide some relief for patients suffering from IL-17-associated diseases.

Regnase-1 acts like a pair of scissors, chopping up inflammation-associated [gene products](#) so they can't be expressed. By targeting genes turned on in response to inflammation, Regnase-1 prevents the body's immune system from going haywire. However, through a process called phosphorylation, Regnase-1 is modified and thus its activity is abolished, allowing the expression of target genes. While [external stimuli](#) were known to activate this modification, previous studies had not determined exactly how phosphorylation occurs.

By altering or deleting Regnase-1 phosphorylation sites in mice, the researchers set about determining why phosphorylation was induced and how this process contributes to the regulation of IL-17-associated inflammation.

Interestingly, the researchers found that IL-17 can trigger the phosphorylation of Regnase-1, resulting in excessive inflammation.

Lead author of the study, Hiroki Tanaka, explains: "Using the mouse models, we showed that Regnase-1 is phosphorylated in response to IL-17 stimulation. The phosphorylated protein is expelled into the cytosol, where it can no longer interact with its target gene products."

This loss of interaction means that the target [genes](#) are expressed,

causing inflammation. However, the two mutant mouse lines showed a reduction in IL-17-induced [inflammation](#), along with decreased disease severity in an experimental model of autoimmune encephalomyelitis.

"Our results confirm that phosphorylation of Regnase-1 plays an important role in the regulation of various inflammatory responses," says senior author Shizuo Akira. "Based on these findings, we propose that Regnase-1 plays a critical role in the development of IL-17-mediated inflammatory diseases. This is exciting because it means that we may be able to design therapeutic agents that block the [phosphorylation](#) of Regnase-1, which may prove effective in the treatment of IL-17-associated autoimmunity."

More information: Hiroki Tanaka et al, Phosphorylation-dependent Regnase-1 release from endoplasmic reticulum is critical in IL-17 response, *The Journal of Experimental Medicine* (2019). [DOI: 10.1084/jem.20181078](#)

Provided by Osaka University

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