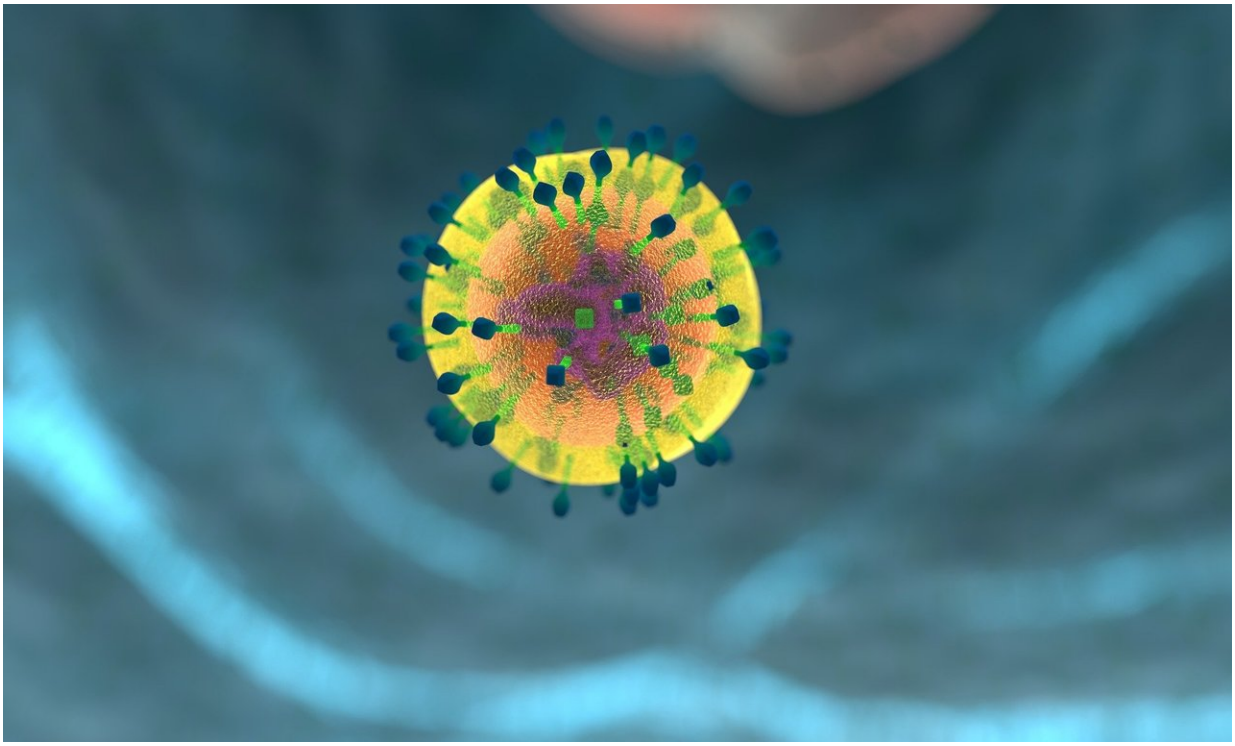
# Phosphorylation of Regnase-1 lets IL-17 run amok

June 3 2019



Credit: CC0 Public Domain

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