Examining the immune response to parasitic worms

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O-GlcNAc glycosylation (alarm hand) senses helminth infection, activates STAT6 (hammer), and in turn alarms immune cells via cytokine secretion. Credit: Artwork by Lan-Tao Gou.

According to the World Health Organization, more than 1 billion people are infected with parasitic helminths worldwide, but the prevention and treatment of helminth infection remain challenging. Research led by the University of Minnesota Medical School looked at if exposure to pathogens, in particular helminths, can stimulate the immune system and reduce predisposition for inflammatory bowel disease (IBD).

"We know that intestinal epithelial cells are first responders to invading gut parasites, through secreting cytokines that alarms and guides immune cells for worm expulsion," said Hai-Bin Ruan, Ph.D., an assistant professor at the U of M Medical School. "We found that a unique glycosylation within epithelial cells, termed as O-GlcNAcylation, can be activated during helminth infections to orchestrate alarmin secretion and facilitate anti-helminth immune responses."

There is a growing interest in the use of helminth therapy for IBD, but clinical data have been inconclusive and the direct use of helminths has obvious safety and efficacy concerns. A greater understanding of host defense mechanisms against helminths is essential for the development of effective and safe treatments for intestinal infections and inflammation.

Published in *Immunity*, the study found that:

- O-GlcNAc glycosylation modifies and activates the STAT6 protein, a master transcriptional regulator of the type 2 anti-helminth immunity;
- STAT6 O-GlcNAcylation in epithelial cells alarms immune cells by instructing intestinal stem cells to make more "tuft cells" and epithelial cells to form membrane pores (composed of GSDMC proteins) to meditate alarmin cytokines; and,
- GSDMC is induced and activated in IBD preclinical models.

"Our study established a novel post translational regulatory switch to turn on epithelial alarmin responses to fight helminth infections," said Ruan.

The research team plans to investigate how O-GlcNAc glycosylation is activated by helminth infections and how GSDMC protein is cleaved to form active membrane pores in human IBD in the future.

More information: Ming Zhao et al, Epithelial

STAT6 O-GlcNAcylation drives a concerted anti-helminth alarmin response dependent on tuft cell hyperplasia and Gasdermin C, *Immunity* (2022). DOI: 10.1016/j.immuni.2022.03.009

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