The yin and yang of inflammation controlled by a single molecule

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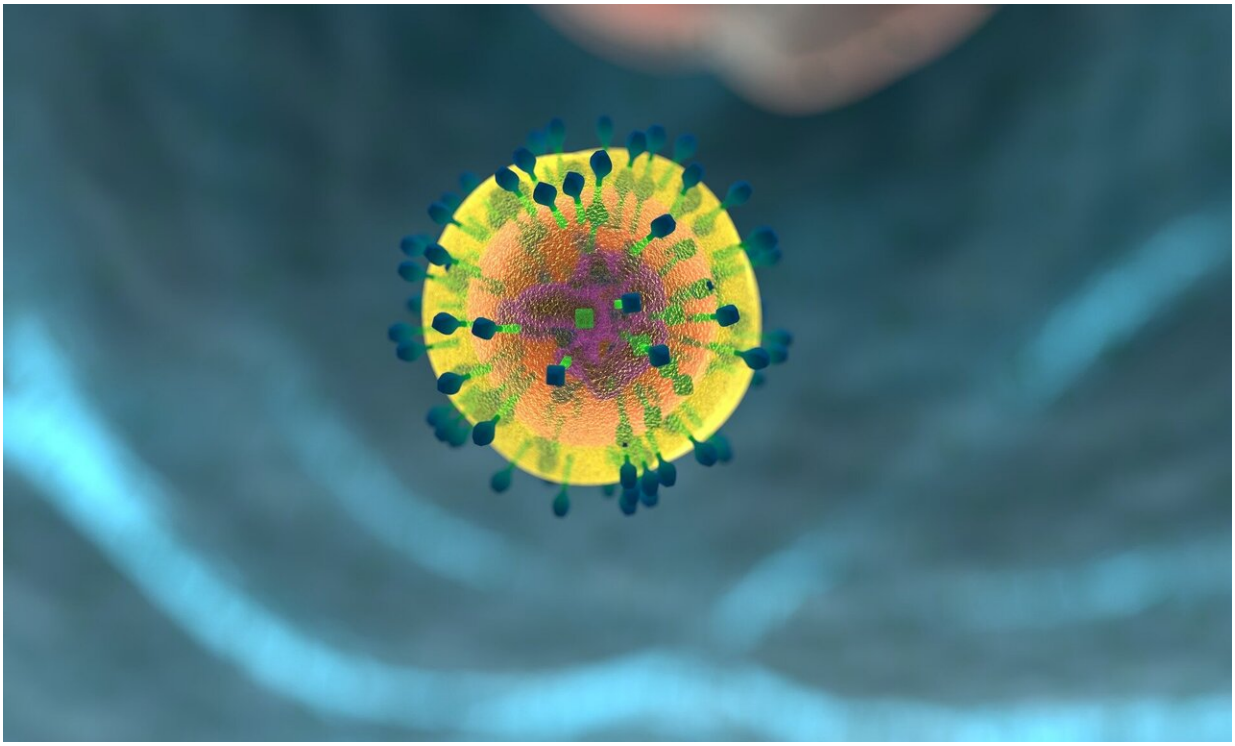

Suzanne Judd, Ph.D., an epidemiologist at UAB, explains what will lead to herd immunity and why it is important to remain vigilant in reducing the spread of COVID-19. Credit: CC0 Public Domain

Researchers from the Perelman School of Medicine at the University of Pennsylvania have now identified a protein called histone deacetylase 3 (HDAC3) as the orchestrator of the immune system's inflammation

response to infection. By using both specially cultured cells and small animal models, HDAC3 was found to be directly involved in the production of agents that help kill off harmful pathogens as well as the restoration of homeostasis, the body's state of equilibrium. This work, published in *Nature*, shows that some of the methods being tested to fight cancer and harmful inflammation, such as sepsis, that target molecules like HDAC3 could actually have unintended and deadly consequences.

"Our work shows that HDAC3 is key to the innate immune response due to the yin and yang of its responsibilities—both triggering and reducing inflammation," said senior author Mitchell A. Lazar, MD, Ph.D., director of the Institute for Diabetes, Obesity, and Metabolism (IDOM). "Now that we understand this, it is now much clearer what needs to be targeted when medications are tested and used to counter potentially deadly inflammation."

Inflammation is a highly complex defense mechanism employed by the innate immune system, meaning that it's something someone is born with and not acquired later like other parts of the immune system. Although inflammation is famous for the appearance of swelling, it also includes changes in blood flow and blood vessel permeability and the migration of white blood cells. When well-orchestrated, the inflammatory response should quickly and precisely locate and eliminate danger before subsiding to anti-inflammatory processes that help with the removal of damaged tissues so that the body can begin to heal and repair.

However, the body's inflammation response could also damage it. Hence, when this rise-and-fall in inflammatory factors go unchecked, diseases like cancer, heart disease, diabetes and even COVID-19 can be developed. Too much inflammation can cause things like septic shock, which causes multiple organ failures within the body due to an uncontrolled "cytokine storm", a phenomenon also widely reported in

patients infected with COVID-19.

Thus, the discovery of HDAC3 as an inflammatory orchestrator has widespread implications. In the study, the researchers used multiple advanced genomic technologies to isolate and locate HDAC3. This protein functions largely as an enzyme, which is a catalyst that brings on different reactions in the body. The team was able to discover the mechanism by which it switches between its different enzymatic states, an ability that allows it to both activate and repress inflammation response, a yin and yang type of existence.

To test what the enzyme did practically, the researchers looked at how mouse models responded to a toxin in three different ways. First, they looked at models lacking HDAC3 in their macrophages, the cells that the immune system uses to destroy harmful presences within the body. There, high levels of protection against the infectious toxin were observed. In different models, when HDAC3 was present and allowed to operate its typical enzyme functions, there was moderate protection and a mortality that aligned with what was expected when this type of toxin was present. But in the third model, when HDAC3's enzyme activities were totally blocked by replacing it with a mutant form of itself, lethality went through the roof and sepsis set in.

"We showed that it's the non-enzymatic functions of HDAC3, previously under-appreciated, that are responsible for the production of the cytokine storm and increased lethality," said the study's lead author, Hoang C. B. Nguyen, an MD/Ph.D. student in the Lazar Lab at the Perelman School of Medicine. "The enzymatic functions of HDAC3 on the other hand, actually help 'quench' the non-enzymatic functions. When the non-enzymatic functions exist in isolation, it's unchecked and harmful."

It's important to note that this all only applies to HDAC3 in

macrophages. While a lack of HDAC3 molecules in those immune system cells produced the best result, efforts to totally remove it from the human body could be disastrous, as it helps form cells the body needs to live.

Moving forward, the researchers hope that their work will inform work being done on the pharmaceutical level. There has been a focus on HDAC inhibitors as a method to fight cancer and inflammation.

"It has been the tradition to target the enzymatic functions of HDAC molecules for decades, but we want to bring attention to the non-enzymatic functions that should be targeted instead," Nguyen said. "In the words of Confucius himself, who introduced the Yin and Yang system of philosophy, 'Do not use a cannon to kill a mosquito,' as it might do more damage than good."

Presently, the findings of this study may also have some implications for treating COVID-19, as some of the patients with it appear to suffer from septic-like conditions.

"The toxin used in this study produces an inflammatory 'cytokine storm,' very similar to what has been seen in severe COVID-19 infections," Lazar said. "If a human cytokine storm is like the mouse, our research suggests that targeting the HDAC3 protein rather than its enzyme activity might mitigate the lethality of the virus."

More information: Dichotomous engagement of HDAC3 activity governs inflammatory responses, *Nature* (2020). DOI: 10.1038/s41586-020-2576-2 , www.nature.com/articles/s41586-020-2576-2

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