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Simulating amino acid starvation may improve dengue vaccines

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Eating a low-calorie diet can help you live longer and prevent age-related diseases—and even improve the immune system's function. A new study finds that, in mice, a compound used in herbal medicine can give a

similar immune boost if given before vaccination—no dieting required.

In a new paper in *Science Signaling*, researchers at the University of Hyderabad in India and the Cornell University College of Veterinary Medicine show that a plant-based compound called halofuginone improves the immune response to a potential vaccine against dengue virus. Halofuginone tricks the body into thinking it is starving for amino acids, which activates a pathway that results in more, and better, antibodies that are better at neutralizing the virus.

The compound could ultimately be part of a strategy to improve the effectiveness of vaccines for diseases such as dengue, which have been difficult to control.

The research group was led by Avery August, Cornell vice provost for academic affairs, professor of immunology and a Howard Hughes Medical Institute professor. Collaborators included Weishan Huang, adjunct assistant research professor of microbiology and immunology; Nooruddin Khan, assistant professor of biotechnology at the University of Hyderabad in India; and doctoral students Sabrina Solouki and Jessica Elmore, both of the August lab.

From previous studies, the team knew that halofuginone activates a pathway called the amino acid starvation response, which normally kicks in when the body is starved of proteins. Restricting calories can have multiple impacts on the immune system, and the researchers wanted to know how artificially activating this pathway would affect immune response to a vaccine.

Halofuginone is a component of an herb used in Chinese medicine. It shows potential for treating muscular dystrophy, autoimmune disease and certain cancers, and appears to have few side effects. It mimics amino acid starvation in the body by blocking the enzyme that links

amino acids to the molecules that deliver them to the site of protein production.

The World Health Organization lists dengue among its top 10 threats to global health, and about half the world's population is at risk of contracting the virus. It is transmitted by mosquitoes and causes flu-like symptoms in most people, but in about 20% of cases, the infection progresses into severe dengue, which can cause shock, hemorrhaging and death.

The virus has been especially difficult to control, in part because there is no vaccine suitable for individuals who have not already been exposed.

In the current study, researchers injected some mice with halofuginone and some with an innocuous salt solution, then inoculated all of the mice with a potential dengue vaccine. Then they looked for differences in the immune response to the vaccine in the two groups.

Mice that received halofuginone produced twice as many antibodies against the virus compared with mice that only received the vaccine, and these antibodies bind to dengue viral components more strongly. Mice don't contract dengue, so the researchers couldn't test whether they were protected. But when they tested the efficacy of the antibodies against dengue virus in a test tube, they saw that halofuginone resulted in antibodies that more effectively neutralized the virus.

"We were particularly surprised by the quality of the antibody response, which is the important part," August said. "In this case the actual affinity of the antibodies for the virus particles was enhanced by the halofuginone."

Furthermore, the researchers showed that halofuginone works specifically by encouraging the formation of germinal centers in the

lymph nodes and spleen. Germinal centers act like factories to produce the B cells that pump out antibodies, and memory B cells that persist for decades and restart antibody production if the invader returns.

"This pathway hasn't before been thought of as one that can regulate enhancing vaccine memory," said August. "It allows us potentially to enhance the body's memory specifically for that vaccine."

Halofuginone worked equally well to enhance the immune response against the four types of dengue virus, but this approach likely would boost any vaccine.

This study primarily focused on B cells that produce antibodies against invading pathogens, but now August's group and their collaborators are examining the specific effects of halofuginone on the response of T cells, which detect the presence of invaders, kill infected cells and signal B cells to create antibodies.

Overall, the findings suggest that investigating drugs that mimic starvation may be a promising area of research for finding strategies to enhance vaccine effectiveness, especially for dengue and other diseases that still lack approved vaccines.

More information: Sumbul Afroz et al. Amino acid starvation enhances vaccine efficacy by augmenting neutralizing antibody production, *Science Signaling* (2019). DOI: 10.1126/scisignal.aav4717

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