Stopping lethal lung damage from the flu with a natural human protein

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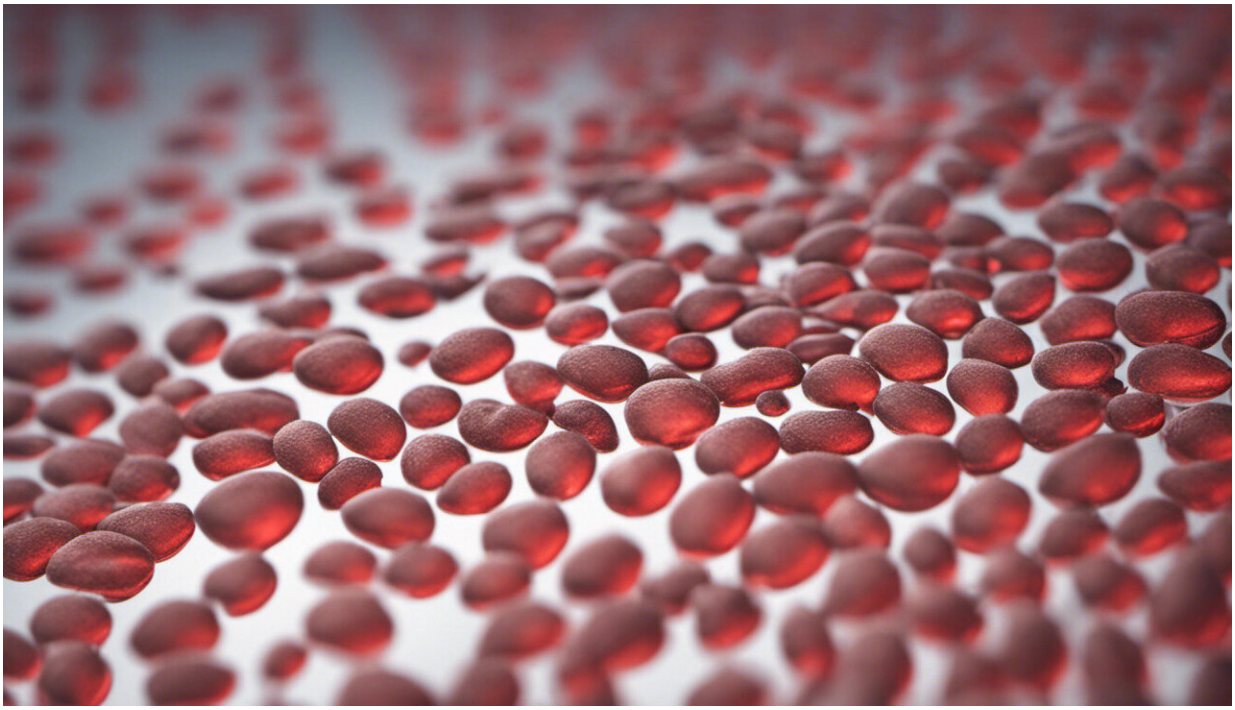

Credit: AI-generated image (disclaimer)

The raging lung inflammation that can contribute to death from the flu can be stopped in its tracks by a drug derived from a naturally occurring human protein, a new animal study suggests.

In mouse studies, all untreated animals given a lethal dose of influenza

died within days. All but one of the infected mice treated with the experimental therapy not only survived, but remained energetic and kept weight on—despite having high levels of the flu virus in their lungs.

The experimental treatment is a heavy dose of MG53, part of a family of proteins that plays an essential role in cell membrane repair. Already identified as a potential therapy for conditions ranging from Alzheimer's disease to persistent skin wounds, MG53 was found in this study to prevent death from a lethal flu infection by blocking excessive inflammation—without having any effect on the virus itself.

The researchers are currently testing the effects of the therapy in mice infected with SARS-CoV-2, the coronavirus that causes COVID-19.

"I haven't ever seen anything like this before," said Jacob Yount, associate professor of microbial infection and immunity at The Ohio State University and co-lead author of the study. "Even though these mice had the same viral load as the untreated mice, they didn't get very sick—with the lethal dose of the flu."

Yount, whose lab studies the immune response against viral infections, co-led the work with Jianjie Ma, professor of cardiac surgery at Ohio State, who discovered MG53 and its role in cell repair and has been developing the protein as a therapeutic agent.

The paper was published online Oct. 8 in the *American Journal of Respiratory and Critical Care Medicine*, and will appear in a future print issue.

The collaboration between the two labs in Ohio State's College of Medicine on this work grew out of a proposal by Matthew Sermersheim, a graduate student in Ma's lab, to expand on the investigation of MG53's links to inflammation. In the July 17 issue of *Nature Communications*,

Sermersheim was the first author of a study showing that the lungs of mice lacking the MG53 gene and infected with flu responded with extensive inflammation compared to normal mice—indicating that MG53 has a protective role in the immune response.

For this new work, the scientists put MG53 to the test against influenza, which, along with other respiratory viruses, is a top-10 cause of death worldwide.

The researchers infected mice with a dose of an H1N1 strain of influenza and treated half with a placebo. Using recombinant human MG53, a molecule Ma's lab has been developing as a drug, the researchers treated the other half of mice with seven daily injections beginning 24 hours after infection. The untreated mice showed an aggressive loss of weight and died within nine days, but 92% of the treated mice lost very little weight, remained active and returned to their normal weight by two weeks after infection.

"The protein has a way to recognize tissue that's been injured and it can go there directly," Ma said. "We are basically enhancing a natural anti-inflammatory mechanism in the body so that when you face the crisis of an aggressive virus infection, the body can better defend itself."

Despite the strikingly different outcomes, the viral loads in both sets of mice were similar—meaning an MG53-based agent is not an anti-viral drug. Even teeming with the flu virus, the airways of treated mice showed little tissue damage.

Though the team is still working to fully identify how this protection occurs, the researchers determined that MG53 stops an immune response mishap called a "cytokine storm," which leads to tissue damage. The research also showed that MG53 mitigates an infection-related cell-death process called pyroptosis, which also promotes inflammation and lung

dysfunction.

"A lot of the lung damage with the flu virus is actually caused by excessive inflammation from our own immune response," Yount said. "If you can dampen that hyperactive immune response, you'll have less tissue damage, even though the virus is still replicating at really high levels."

Lung tissue damaged by inflammation is deadly because it allows fluid and cells to build up in airways, preventing the lungs from absorbing oxygen.

Ma's previous work in animal models suggests driving up levels of MG53 in the body for therapeutic purposes is safe: Mice his lab has genetically engineered to over-produce the protein live longer and healthier lives than normal mice. Though the scientists envision MG53 as part of a cocktail of drugs targeting deadly viral infections, they caution that much more research is needed before a therapy is available for humans.

"We need better anti-inflammatory tissue repair therapies," Ma said. "We don't have COVID-19 data yet, but even with influenza, which hits us on a seasonal basis, this application could make quite a bit of difference."

More information: Adam D. Kenney et al. Recombinant MG53 Protein Protects Mice from Lethal Influenza Virus Infection, *American Journal of Respiratory and Critical Care Medicine* (2020). DOI: 10.1164/rccm.202007-2908LE

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