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MERS-CoV treatment effective in monkeys, study finds

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Treatment with two common drugs reduced viral replication and lung damage when given to monkeys infected with the virus that causes Middle East Respiratory Syndrome. The condition is deadly pneumonia that has killed more than 100 people, primarily in the Middle East.

Middle East Respiratory Syndrome, or MERS, was first reported in Saudi Arabia last year. The infection is caused by a coronavirus, called MERS-CoV, which is closely related to several coronaviruses that infect bats. About half of patients who developed the syndrome have died. Currently, there is no proven effective treatment.

The new findings show that a combination of interferon-alpha 2b and ribavirin, drugs routinely used to treat hepatitis C, may be an effective treatment for MERS-CoV infection, said Dr. Angela L. Rasmussen, a research scientist in the Department of Microbiology at the University of Washington in Seattle and co-author of the study.

"Because these two drugs are readily available, they could be used immediately to treat patients infected with MERS-CoV," Rasmussen said.

The study was conducted by researchers from the U.S. National Institute of Allergy and Infectious Diseases; the Universite Pierre et Marie Curie in Paris, France; the University of Manitoba in Winnipeg, Canada; and the University of Washington in Seattle. The results were published online September 8 by the journal *Nature Medicine*. Darryl Falzarano, of

the National Institute of Allergy and Infectious Diseases's Rocky Mountain Laboratory in Hamilton, Mont., was the paper's lead author.

Instead of directly targeting the virus like most conventional antivirals, these drugs work primarily by moderating the body's immune response to the virus and by promoting repair of damaged lung tissue, said Rasmussen.

Working with the team of scientists in the UW Viromics Lab, led by Dr. Michael Katze, UW professor of microbiology, Rasmussen and her colleagues watched how the lung cells responded to the new treatment by tracking their gene expression profiles.

They did this by studying RNA extracted from the infected monkeys' lungs to track changes in what is called the transcriptome. When a cell needs to use a gene, it copies the gene's DNA-encoded instructions into RNA. That RNA transcript is then read to direct the assembly of a protein. By using a "lab on a chip" technology, called a microarray, it is possible to detect and measure RNA transcripts from all the genes in a population of cells. By analyzing the transcriptome, it is then possible to track how cells or a tissue respond to infection, a drug, or some other stimulus. In this case, it allows researchers to study the host response to MERS-CoV in the context of the entire complex biological system, rather than one gene at a time.

Treatment with interferon-alpha 2b and ribavirin appeared to have several interesting effects. The combination increased the transcription of genes that fight viral infections, for example, and reduced transcription of genes that promote inflammation. Of particular interest to Rasmussen and her colleagues, however, was the finding that treatment increased the transcription of genes that assist in regulating a protein called sonic hedgehog.

The sonic hedgehog protein helps moderate the immune response so that it targets the virus more precisely. This honing in reduces collateral damage from broader, less discriminate attack, and helps stimulate repair and growth of lung tissue.

During infection with many severe respiratory viruses, such as influenza, much of the damage is done, not by the virus, but by the body's uncontrolled immune response to the virus, Rasmussen said.

The findings of this new study suggest that, in the case of MERS-CoV infections, interferon-alpha 3b and ribavirin may work primarily by reducing damaging inflammation of the lung and promoting healing by altering the host response, rather than directly targeting the virus.

If that is the case, other drugs that can similarly modulate the body's reaction to viral infections may also prove to be effective against MERS-CoV and other infectious agents, she said.

More information: Falzarano et al. Interferon-a2b and ribavirin treatment improves outcome in MERS-CoV-infected rhesus macaques. *Nature Medicine* DOI: 10.1038/nm.3362 (2013).

Falzarano et al. Inhibition of novel human coronavirus-EMC replication by a combination of interferon-alpha2b and ribavirin. *Scientific Reports* DOI: 10.1038/srep01686 (2013).

Munster et al. Novel human coronavirus causes pneumonia in a macaque model resembling human disease. *New England Journal of Medicine* DOI: 10.1056/NEJMc1215691 (2013).

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