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Scientists engineer strain of MERS coronavirus for use in a vaccine

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Scientists have developed a strain of the Middle East respiratory syndrome coronavirus (MERS-CoV) that could be used as a vaccine against the disease, according to a study to be published in *mBio*, the online open-access journal of the American Society for Microbiology. The mutant MERS virus, rMERS-CoV-ΔE, has a mutation in its envelope protein that makes it capable of infecting a cell and replicating its genetic material, but deprives it of the ability to spread to other tissues and cause disease. The authors say once additional safe guards are engineered into the virus, it could be used as the basis of a safe and effective live-attenuated vaccine against MERS.

"Our achievement was a combination of synthetic biology and genetic engineering," says co-author Luis Enjuanes of The Autonomous University of Madrid (Universidad Autónoma de Madrid).

"The injected vaccine will only replicate in a reduced number of cells and produce enough antigen to immunize the host," he says, and it cannot infect other people, even those in close contact with a vaccinated person.

Since MERS was first identified in June 2012, the World Health Organization has been notified of 108 cases of infection, including 50 deaths. Although the total number of cases is still relatively small, the case fatality rate and the spread of the virus to countries beyond the Middle East is alarming to public health officials. If the virus evolves the ability to transmit easily from person to person, a much more widespread

epidemic is possible. Diagnostic assays and antiviral therapies for MERS have been described, but reliable vaccines have not yet been developed.

Enjuanes and his team applied what they had learned from 30 years of research on the molecular biology of coronaviruses to synthesize an infectious cDNA clone of the MERS-CoV genome based on a published sequence. They inserted the viral cDNA chromosome into a bacterial artificial chromosome, and mutated several of its genes, one by one, to study the effects on the virus' ability to infect, replicate, and re-infect cultured human cells.

Mutations that disabled accessory genes 3, 4a, 4b and 5 did not seem to hinder the virus: mutant viruses had similar growth rates as the wild-type virus, indicating that the mutations do not disable the virus enough to deploy the mutants in a vaccine. Mutations in the envelope protein (E protein), on the other hand, enabled the virus to replicate its genetic material, but prevented the virus from propagating, or infecting nearby cells.

A large amount of the rMERS-CoV-ΔE virus would be needed for a live attenuated MERS vaccine. A virus that can't propagate itself would be unable to grow the volume needed without help. Enjuanes says they provided the virus with a supplemental form E protein.

"To grow the virus, we create what are called 'packaging cells' that express the E protein missing in the virus. The gene to encode this protein is integrated in the cell chromosomes and will not mix with the viral genes. Therefore, in these cells, and only within them, the virus will grow by borrowing the E protein produced by the cell," says Enjuanes. "When the virus in administered to a person for vaccination, this person will not be able to provide the E protein to the defective virus," so the virus will die off after producing antigens to train the human immune system to fight a MERS-CoV infection.

Enjuanes says rMERS-CoV-ΔE is a very promising vaccine candidate, but more work remains before they can start clinical trials. He says the mutation in the E protein that prevents the virus from propagating represents one safe guard, but the US Food and Drug Administration requires that a recombinant live attenuated vaccine strains include at least three safe guards to ensure the virus doesn't revert easily back to its virulent form. His group is currently working on introducing other disabling mutations in genes that are located in regions of the virus' genome that are far away from the E protein gene to ensure the virus cannot revert back to virulence in a single recombination event.

Provided by American Society for Microbiology