Mammals defend against viruses differently than invertebrates

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Biologists have long wondered if mammals share the elegant system used by insects, bacteria and other invertebrates to defend against viral infection. Two back-to-back studies in the journal *Science* last year said the answer is yes, but a study just published in *Cell Reports* by researchers at the Icahn School of Medicine at Mount Sinai found the opposite.

In the Mount Sinai study, the results found that the defense system used by invertebrates—RNA interferences or RNAi—is not used by mammals as some had argued. RNAi are small molecules that attach to molecular scissors used by invertebrates to cut up invading viruses.

Mammals use a form of RNAi to fine-tune the expression of hundreds of genes that coordinate development in the womb, says the study's senior author, Benjamin tenOever, PhD, Fishberg Professor in the Department of Medicine and Department of Microbiology at the Icahn School of Medicine at Mount Sinai. But it has never been clear that adult mammals use RNAi the same way that plants and insects do, he says. "Mammals have cell machinery that looks capable of producing RNAi to fight virus, but we believe it only helps to produce different small RNA products called microRNAs, which are not antiviral," Dr. tenOever says.

The correct answer matters because RNAi is being studied as a potential basis for new kinds of drugs for the treatment of hemophilia, beta-thalassemia and many viral infections, says Dr. tenOever.

"We believe our results settle a longstanding debate about whether mammals, including humans and mice, fight viruses using RNAi, and the answer is good news," he says. "Drug designers interested in using RNAi to treat disease have worried that if RNAi is part of the mammalian response to viral infections, RNAi-based agents could compromise a human's immune response, producing unintended consequences. That is not a concern now, based on our findings."

Mammals are known to fend off viruses with a system based on interferons, signaling proteins made by immune cells that amplify the body's attack on invaders. The finding that mammals do not use RNAi to fight viruses suggests that RNAi-based drugs could augment the existing interferon response in mammals, Dr. tenOever says. "We could harness this potent RNAi viral-killing machine when natural human immunity isn't enough."

To answer the question, a team of researchers from the Icahn Graduate School of Biomedical Science used a virus that produces oral lesions in cows and pigs. They eliminated the part of the virus that causes disease, rendering it harmless and susceptible to both RNAi and interferons. They then took this harmless virus and gave it the capacity to block either interferon or RNAi.

In experiments with mice, when the virus was designed to block interferon, no immune defense occurred and the interferon-blocking virus flourished. In contrast, giving the virus the capacity to block RNAi, found that the animals mounted a robust interferon-based defense that further weakened the RNAi-blocking virus. The same thing happened when the RNAi-blocking virus was introduced to engineered mice that could not produce interferons. "If mammals used interferon and RNAi to fight the virus, we would have seen the RNAi-blocking virus flourish in at least this setting—but we did not," Dr. tenOever says. "This is the strongest published data that argues against recent claims that RNAi

exists in mammals, he says.

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