# Mammalian body cells lack ancient viral defense mechanism

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A team led by Chris Sullivan, a professor of molecular biosciences at The University of Texas at Austin, has provided the first positive evidence that RNA interference (RNAi), a biological process in which small RNA molecules prevent genes from being expressed, does not play a role as an antiviral in most body, or "somatic," cells in mammals.

Their research was published in *Cell Host & Microbe*.

RNAi plays an important antiviral role in plants and invertebrates, but it has long been disputed whether it plays a similar role in mammals. A better understanding of how RNAi works could lead to improved strategies for treating viral disease.

"What we've demonstrated, at least in a lab setting, is that when we introduce a virus to mammalian cells, the RNAi machinery actually gets turned down," said Sullivan. "That's the opposite of what you'd expect if it were playing an antiviral role."

This important finding emerges from years of contentious debate among scientists – a debate that isn't quite over yet. Two new papers published in *Science* offer counter evidence, showing that there is RNAi antiviral activity in some mammalian cells.

"It's not just an academic controversy," said Sullivan. "If we can learn to manipulate and modify RNAi within our own cells, that may prove to be the best path to effective genetic therapies for a host of diseases. But we

need to understand what regulates RNAi to fully realize its promise."

Sullivan said there is a likely explanation for the apparent conflict between his findings and those published in *Science*. "Its possible that everyone is correct, but we are looking in different cell types," he said.

The *Science* papers describe experiments in stem cells, while Sullivan and his colleagues, including professor Bob Krug, are studying "somatic" cells that make up most of our body.

"Our somatic cells have evolved extremely robust, protein-based anti-viral defenses of a kind that plants and invertebrates don't tend to have," said Sullivan. "So maybe in that context RNAi evolved away from the antiviral role it once played. We don't need it to do that anymore. But we don't have those same defenses in our stem cells, so maybe in that context RNAi still serves an antiviral function."

Sullivan and his colleagues also found evidence to suggest what RNAi may be doing in mammalian somatic cells if it's not antiviral. It may be anti-antiviral. It may have evolved to help regulate the protein-based immune response that superseded it.

"These are powerfully toxic responses our bodies have evolved to deal with infections, including viral infections," said Sullivan. "But the more effective they are when fighting off viruses, the more detrimental they're likely to be when expressed inappropriately, and so the more likely it is that they're going to be regulated at multiple levels. Our hypothesis is that once this protein-based response evolved, then the cells repurposed the RNAi machinery to turn off their own genes, to help the cell return to homeostasis when no longer under stress or attack."

Sullivan said it's really too soon to say for sure whether that hypothesis is right. But he added, "All of these combined studies taken together are

key to better understanding RNAi, virus infection, and the very nature of stem cells."

Provided by University of Texas at Austin