More than a machine: Ribosome regulates viral protein synthesis, revealing potential therapeutic target

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Viruses can be elusive quarry. RNA viruses are particularly adept at defeating antiviral drugs because they are so inaccurate in making copies of themselves. With at least one error in every genome they copy, viral genomes are moving targets for antiviral drugs, creating resistant mutants as they multiply. In the best-known example of success against retroviruses, it takes multiple-drug cocktails to corner HIV and narrow its escape route.

Rather than target RNA viruses themselves, aiming at the host cells they invade could hold promise, but any such strategy would have to be harmless to the host. Now, a surprising discovery made in ribosomes may point the way to fighting fatal viral infections such as rabies.

Results were published online November 19 in Proceedings of the National Academy of Sciences.

The ribosome has traditionally been viewed as the cell's molecular machine, automatically chugging along, synthesizing proteins the cell needs to carry out the functions of life. But Amy Lee, a former graduate student in the program of virology, and Sean Whelan, HMS professor of microbiology and immunobiology, now say the ribosome appears to take a more active role, regulating the translation of specific proteins and ultimately how some viruses replicate.

The researchers were studying differences between how viruses and the host cells they infect carry out the process of translating messenger RNAs (mRNAs) into proteins. Focusing on protein components found on the surface of the ribosome, they discovered a protein that some viruses depend on to make other proteins, but that the vast majority of cellular mRNAs do not need.

Called rpL40, this ribosomal protein could represent a target for potential treatments; blocking it would disable certain viruses while leaving normal cells largely unaffected.

"Because certain viruses are very sensitive to the presence and absence of these ribosomal proteins, it might be a useful way for us to think about targeting ribosomes for therapeutic purposes from an antiviral standpoint," said Whelan. "This is a way to think about interfering with rabies virus infection. There are no therapeutics for rabies infection."

The team screened protein constituents of the ribosome to see which ones might be involved in specialized protein synthesis. Studying the vesicular stomatitis virus, a rhabdovirus in the same family as the rabies virus, they found that its mRNAs depended on rpL40 but only 7 percent of host-cellular mRNAs did. Some of the cellular mRNAs that depend upon rpL40 were stress response genes.

Experiments in yeast and human cells revealed that a class of viruses, which includes rabies and measles, depended on rpL40 for replication.

"This work reveals that the ribosome is not just an automatic molecular machine but instead also acts as a translational regulator," said first author Amy Lee, who is now a post-doctoral researcher at the University of California, Berkeley.

The concept of targeting cellular functions such as protein synthesis for

antiviral therapies is being explored by a number of research groups, but there are no drugs based on this.

"We think the principle is bigger than just this single protein," Whelan said. "Viruses have an uncanny way of teaching us new biology all the time."

Provided by Harvard Medical School

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