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Newly Discovered HIV Genome Modification May Put a Twist on Vaccine and Drug Design

Crucial HIV RNA modification called m6A influences viral replication, but wasn't previously taken into consideration when developing anti-HIV therapies

Researchers at University of California, San Diego School of Medicine have discovered that HIV infection of human immune cells triggers a massive increase in methylation, a chemical modification, to both human and viral RNA, aiding replication of the virus. The study, published February 22, 2016 in *Nature Microbiology*, identifies a new mechanism for controlling HIV replication and its interaction with the host immune system.

"We and other colleagues at pharmaceutical companies have worked over the years to develop drugs targeting HIV's genetic material, its RNA, but we never made it to the clinic," said senior author Tariq Rana, PhD, professor of pediatrics at UC San Diego School of Medicine. "Now we know why — we were developing drugs using RNA targets that didn't have these modifications, when in reality the RNA was different."

In human cells, RNA is the genetic material that carries instructions from the DNA in a cell's nucleus out to the cytoplasm, where molecular machinery uses those instructions to build proteins. In contrast, HIV's entire genome is made up of RNA, not DNA. The virus hijacks its host's cellular machinery to translate its RNA to proteins.

Cells can chemically modify RNA to control or alter its function. One of these modifications, known as N6-methyladenosine (m6A), is common in humans and other organisms. But little was known about the role m6A plays in the human immune system, or in the interactions between our cells and invading pathogens, such as HIV.

In the study, Rana's team discovered m6A modifications in HIV RNA for the first time. They also examined m6A's effect on function in both HIV and human host RNA during infection of human immune cells.

“M6A had always been considered a steady modification of cellular RNA. Instead, it turned out to be extremely dynamic and highly responsive to external stimuli, such as viral infections” said Gianluigi Lichinchi, a graduate student in Rana’s lab and first author of the study. “In the future, these findings could aid in improving the design and efficacy of HIV/AIDS vaccines.”

One of the proteins encoded by HIV’s RNA genome is Rev. After Rev proteins are built in the human host cell’s cytoplasm, they move back into the nucleus, where they assemble at a particular point on HIV RNA called the Rev responsive element (RRE). There, Rev helps transport newly produced HIV RNA transcripts into the host cytoplasm. This is an essential step in viral replication.

The team determined that m6A modification of both human and viral RNA influences the interaction between the HIV Rev protein and the RNA RRE. When the researchers silenced the enzyme that removes m6A from RNA, HIV replication increased. Conversely, when they silenced the enzyme that adds m6A to RNA, HIV replication decreased — a finding the researchers say could be exploited pharmacologically to combat the infection.

“The HIV field has missed this modification in physiological RNA structure and HIV genome for more than 30 years,” Rana said. “I will not be surprised if other viruses with RNA genomes also exploit this m6A modification mechanism to evade immune surveillance and control their replication in human cells. These viruses include, for example, influenza, Hepatitis C, Ebola and Zika, just to name a few.”

Study co-authors include Shang Gao, Vikas Bansal, UC San Diego; Yogesh Saletore, Weill Cornell Medical College; Gwendolyn Michelle Gonzalez, Yinsheng Wang, UC Riverside; and Christopher Mason, Weill Cornell Medical College and HRH Prince Alwaleed Bin Talal Bin Abdulaziz Alsaud Institute for Computational Biomedicine, Feil Family Brain and Mind Research Institute.

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