Protein uses two antiviral strategies to ward off infections

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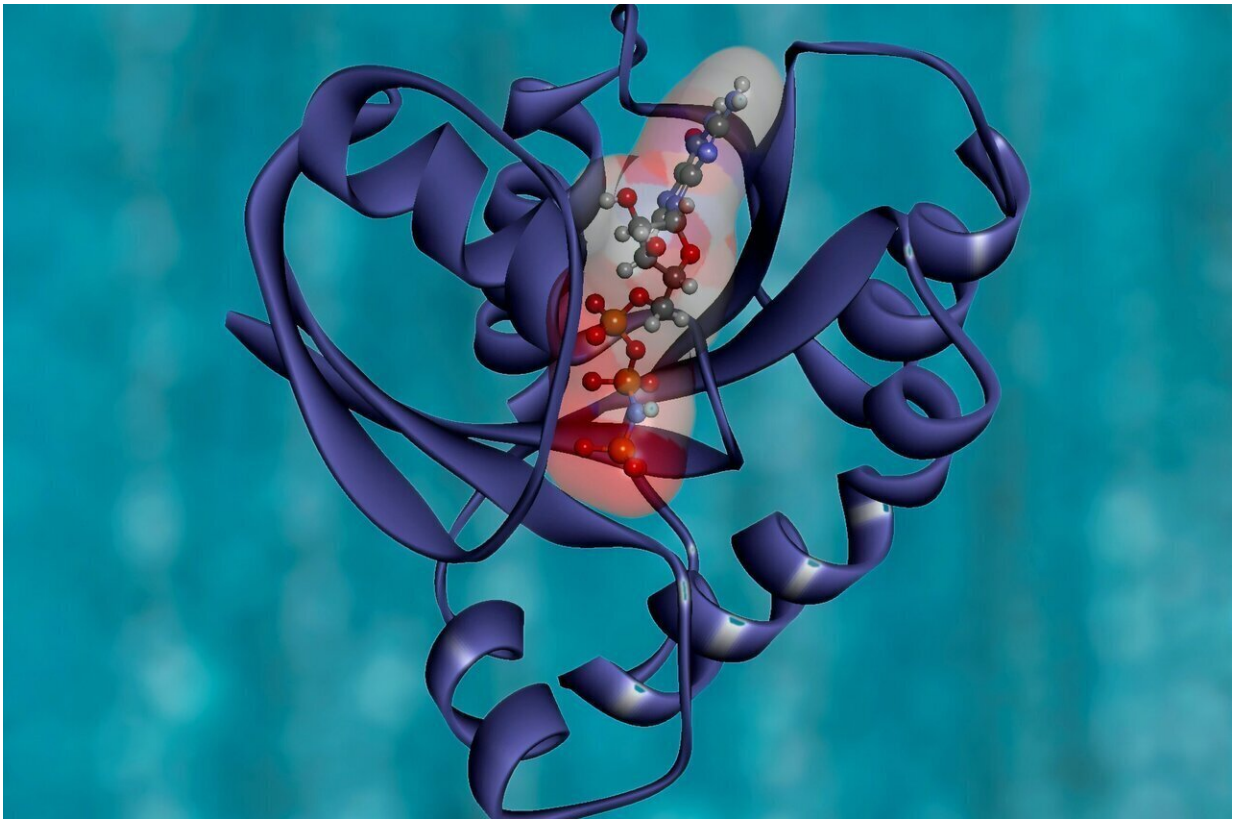

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To protect humans against infection, a protein called MARCH8 tags the vesicular stomatitis virus (VSV) for destruction while it merely holds HIV hostage, a new study in *eLife* shows.

The findings reveal how a single protein can use multiple strategies to defend cells against viral infection. They could also improve our understanding of how HIV overcomes the human immune defense.

Previous studies have shown that MARCH8 stops HIV and VSV from entering human cells by targeting the viral proteins that are essential for these viruses to enter cells. But how the protein does this remained unclear. Researchers in Japan suspected that MARCH8 might flag an important VSV envelope protein for destruction by targeting a particular amino acid called lysine.

"The VSV G-glycoprotein (VSV-G) has a short tail containing five lysines, making it an ideal target," explains senior author Kenzo Tokunaga, Principal Investigator in the Department of Pathology, National Institute of Infectious Diseases, Tokyo, Japan. "The HIV envelope glycoprotein (Env), by contrast, has a very long tail with only two lysines, making it harder for MARCH8 to flag it for destruction."

To test their idea, Tokunaga and his team, including co-first authors and Postdoctoral Fellows Yanzhao Zhang and Takuya Tada, replaced the five lysines on the tail of VSV-G with five arginines—another type of amino acid. They also replaced the two lysines on the tail of HIV Env with two arginines. The change allowed VSV-G to escape MARCH8, but not HIV Env. This suggests that MARCH8 targets HIV Env and VSV-G using two different mechanisms.

Instead of marking HIV Env for destruction, the team found that MARCH8 holds it hostage, inhibiting its ability to make infectious copies of itself (replicate) and spread to other cells. When they created a mutant version of MARCH8 that lacks a specific pattern of the amino acid tyrosine, they found that HIV Env was able to escape, allowing the virus to replicate. This suggests that the tyrosine pattern in MARCH8 is essential to its HIV defense strategy.

"Our work may help explain why humans don't develop symptoms when infected with VSV, even though it can make some animals, mostly cows, horses and pigs, very ill," says Tokunaga. "The findings might also explain, at least in part, why HIV is able to hide from the human immune system, causing persistent infections that are difficult to treat."

More information: Yanzhao Zhang et al, MARCH8 inhibits viral infection by two different mechanisms, *eLife* (2020). DOI: 10.7554/eLife.57763

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