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Discovery of mechanism behind HIV infections could also hold key to COVID-19

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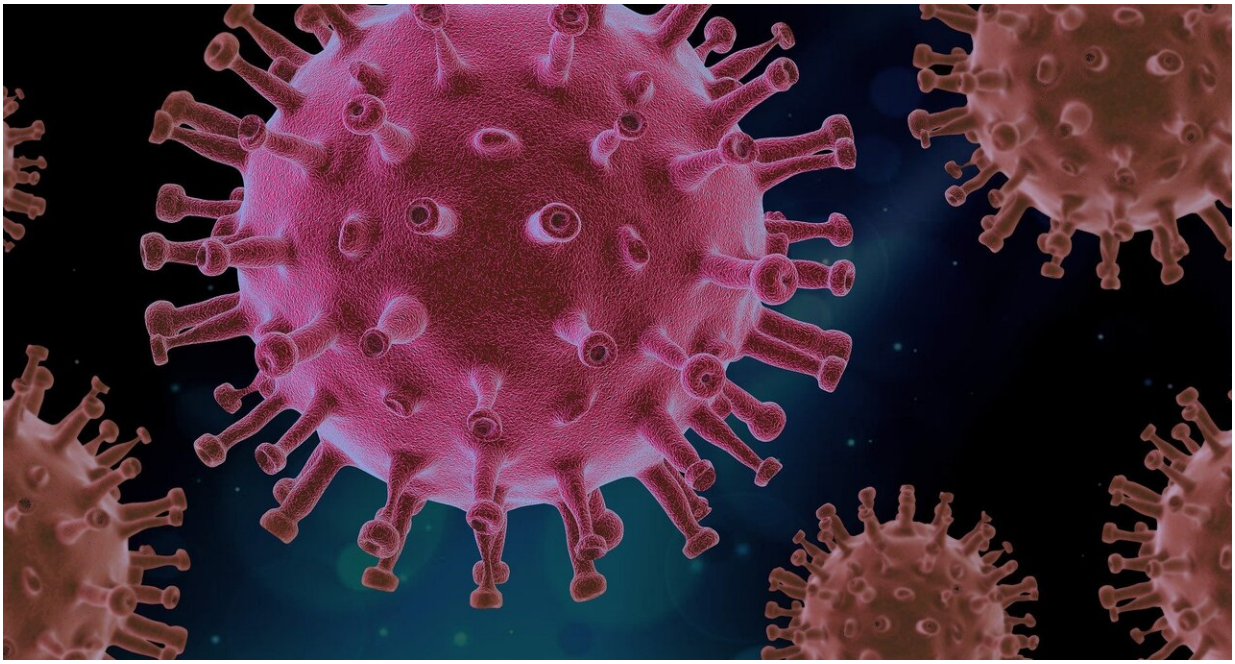

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A newly discovered mechanism at work in human immunodeficiency virus (HIV) patients may also lead to new treatments for COVID-19, according to a team of researchers at the University of Alberta.

The recently published paper in the journal of the American Society for Microbiology, mBio, reveals how HIV attacks peroxisomes, organelles

found in all cells that help regulate the immune system, lipid metabolism and cardiovascular health, brain development and nerve function.

"We know that other viruses, including West Nile virus and Zika virus, have several different mechanisms to reduce peroxisomes as a way to inhibit the production of interferon, which will block most viruses from replicating," said cell biologist Tom Hobman, former Canada Research Chair in RNA Viruses and Host Interactions.

"All viruses have ways to block this interferon response, which fits with the idea that peroxisomes are an important target in terms of virus infections."

The researchers wondered whether SARS-CoV-2, the virus that causes COVID-19, might also attack peroxisomes, so they started testing peroxisome-boosting drugs against the virus in cell cultures.

"What we're looking at is how these drugs can down-regulate replication of the SARS-CoV-2 virus," said Hobman, who is also a member of the Women and Children's Health Research Institute. "We see some very striking results at the early stages."

Uncovering the mechanism behind HIV

Hobman said his laboratory teamed up with neurologist Christopher Power, Canada Research Chair in Neurologic Infection and Immunity, about five years ago to examine why many HIV patients experience premature aging, lipodystrophy (a change in the way the body metabolizes fat), and a range of neurological disorders that can prevent them from living independently.

The team uncovered four microRNAs that are elevated in the brains of HIV patients who have dementia.

"We learned that all four microRNAs that were dysregulated in the brains of these patients targeted the peroxisome biogenesis pathway," he said, "so they all down-regulate the expression of proteins needed to build peroxisomes."

"Peroxisomes are probably not as well studied as they should be, given that they are absolutely essential for health and development in humans," Hobman said, noting that children born with the genetic peroxisomes disorder, Zellweger syndrome, have severe developmental and neurological defects and usually die within a year or two of birth.

Hobman noted the U of A is unusual in having two other laboratories that also focus on peroxisomes, run by cell biology professor Richard Rachubinski and professor and chair Andrew Simmonds.

"This wealth of expertise has been of tremendous benefit to our research program," he said.

Repurposed cancer drugs could be used to target HIV, COVID-19

The Hobman lab demonstrated last year that boosting peroxisomes by manipulating genes can inhibit the replication of the Zika virus. Over the next four months they will continue testing drugs that boost peroxisomes to see whether they can do the same against SARS-CoV-2 and HIV.

Several of the drugs they are trying have been approved as cancer drugs, but Hobman discovered they coincidentally target a pathway that blocks peroxisome formation.

"Many of these drugs have already been tested in humans for other indications, so our work should progress relatively quickly," he said.

He pointed out that several of the promising treatments against COVID-19, including remdesivir and interferon, are relatively expensive and must be given in hospital, whereas some of the peroxisome boosters can be taken orally and have few side-effects.

He said he's excited about the potential for this new approach to fight viral infections.

"The most effective drugs are usually direct-acting antivirals," he said. "The drugs that we're looking at now target the infected cells. Because they don't target the virus itself, it is quite possible that they will have broad-spectrum antiviral activity by interfering with common mechanisms used by multiple viruses."

More information: Zaikun Xu et al. The HIV-1 Accessory Protein Vpu Downregulates Peroxisome Biogenesis, *mBio* (2020). DOI: 10.1128/mBio.03395-19

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