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High-throughput screen identifies potential henipavirus drug target

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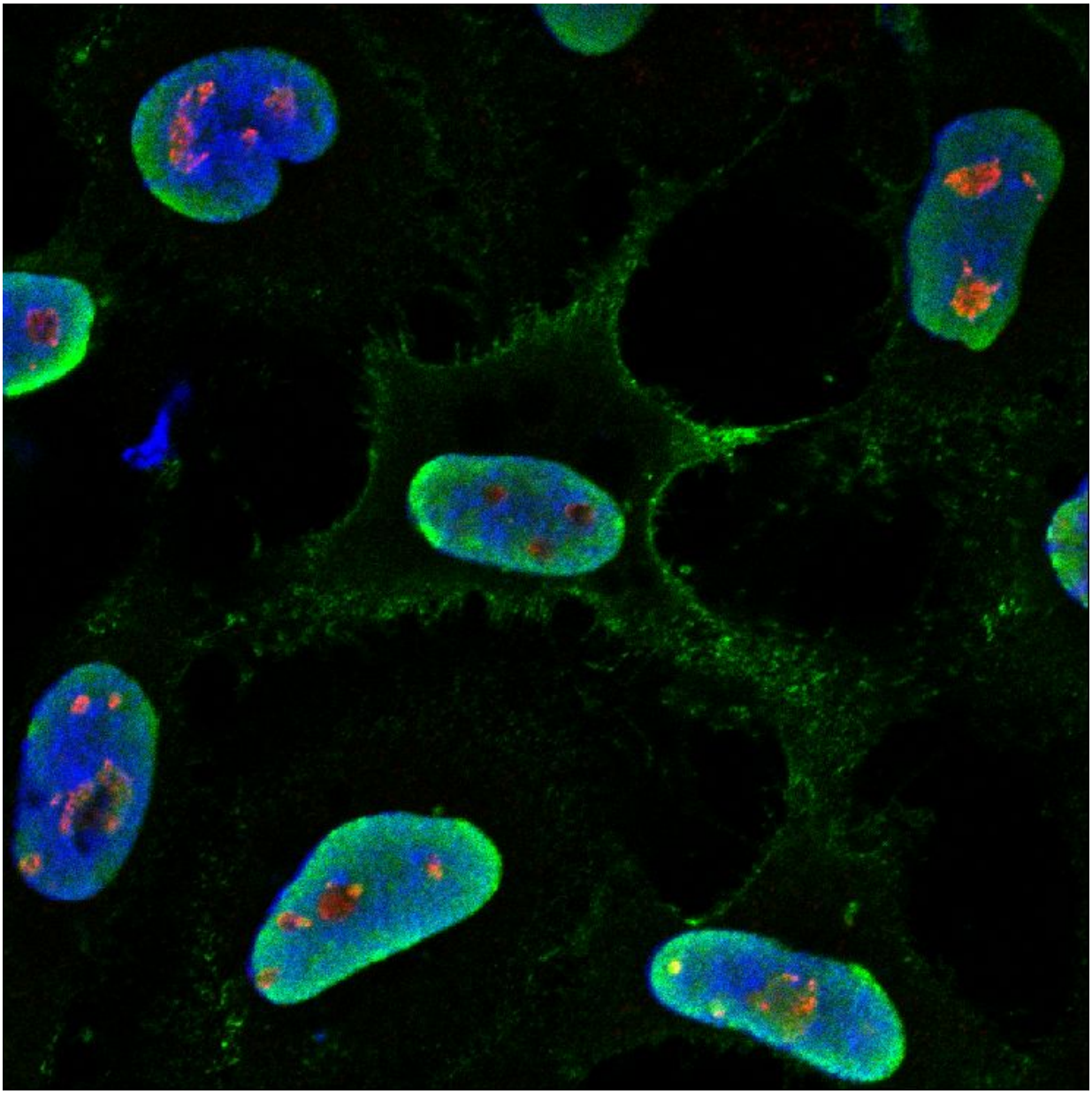

Infection of human cells with Hendra virus (green) is critically dependent on fibrillarin (red), a host protein that resides deep within the cell nucleus (blue). Credit: Deffrasnes C, Marsh GA, Foo CH, Rootes CL, Gould CM, Grusovin J, *et al*. (2016)

The closely related Hendra and Nipah viruses (referred to jointly as henipaviruses) are deadly cousins of the more common mumps, measles, and respiratory syncytial viruses, all members of the paramyxovirus family. Henipavirus outbreaks are on the rise, but little is known about them, partly because research has to be conducted under extreme level containment conditions.

A study published on March 24, 2016 in *PLOS Pathogens* reports the first high-throughput RNA interference screen for host genes that are essential for live henipavirus infection of human cells, and identifies a specific cell protein called fibrillarin as a potential target for drugs against henipaviruses and other paramyxoviruses.

Henipaviruses infection is common in bats, and outbreaks in Australia and Malaysia have been linked to human contact with local fruit bats. No human vaccines or treatments exist, and because of high mortality rates (between 35 and 90% of patients known to be infected died in recent outbreaks) the viruses have been classified as biosafety-level 4 (BSL-4) pathogens the highest biosafety containment level. A multi-disciplinary research team led by Cameron Stewart of the CSIRO Australian Animal Health Laboratory in East Geelong, Victoria, systematically interfered with the function of genes in human cells to identify host genes that are needed for henipavirus infection.

In their initial screen, the researchers identified several hundred human genes whose function was necessary for successful henipavirus infection.

They subsequently honed in on one of them, called fibrillarin, which codes for a protein present in the nucleolus. The nucleolus is the largest structure in the nucleus of mammalian cells and functions as the assembly room for so-called ribosomes which are subsequently exported out of the nucleus into the cytoplasm and become the protein factories of the cell.

To explore possible mechanisms, the researchers examined closely which step of the viral life cycle was blocked by interfering with fibrillarin function. Fibrillarin, they found, is not necessary for viral entry into the host cells but required for the early synthesis of viral RNA. More specifically, the researchers report that mutating the catalytic activity of fibrillarin inhibits henipavirus infection, suggesting that this human enzyme could be targeted therapeutically to combat henipavirus infections.

When they tested whether fibrillarin function was required for successful infection of human cells by other paramyxoviruses, the researchers found that this was indeed the case for all the family members tested, including the mumps and measles pathogens. This raises the potential that drugs that interfere with fibrillarin function might have broader use against all of these viruses.

To their knowledge, the researchers say, the study is the first of its kind to be conducted in a BSL-4 facility. They suggest that it "serves as a blueprint for how high-throughput RNAi screens can be performed under high biocontainment conditions".

They conclude that the study "reveals a previously unappreciated role for nucleolar proteins with methyltransferase activity such as fibrillarin in henipavirus infection, and suggests that methyltransferase enzymes represent a potential target for development of an anti-henipavirus drug".

More information: Deffrasnes C, Marsh GA, Foo CH, Rootes CL, Gould CM, Grusovin J, et al. (2016) Genome-wide siRNA Screening at Biosafety Level 4 Reveals a Crucial Role for Fibrillarin in Henipavirus Infection. *PLoS Pathog* 12(3): e1005478. DOI: 10.1371/journal.ppat.1005478