Study shows high frequency of spontaneous mutation in Ebola virus

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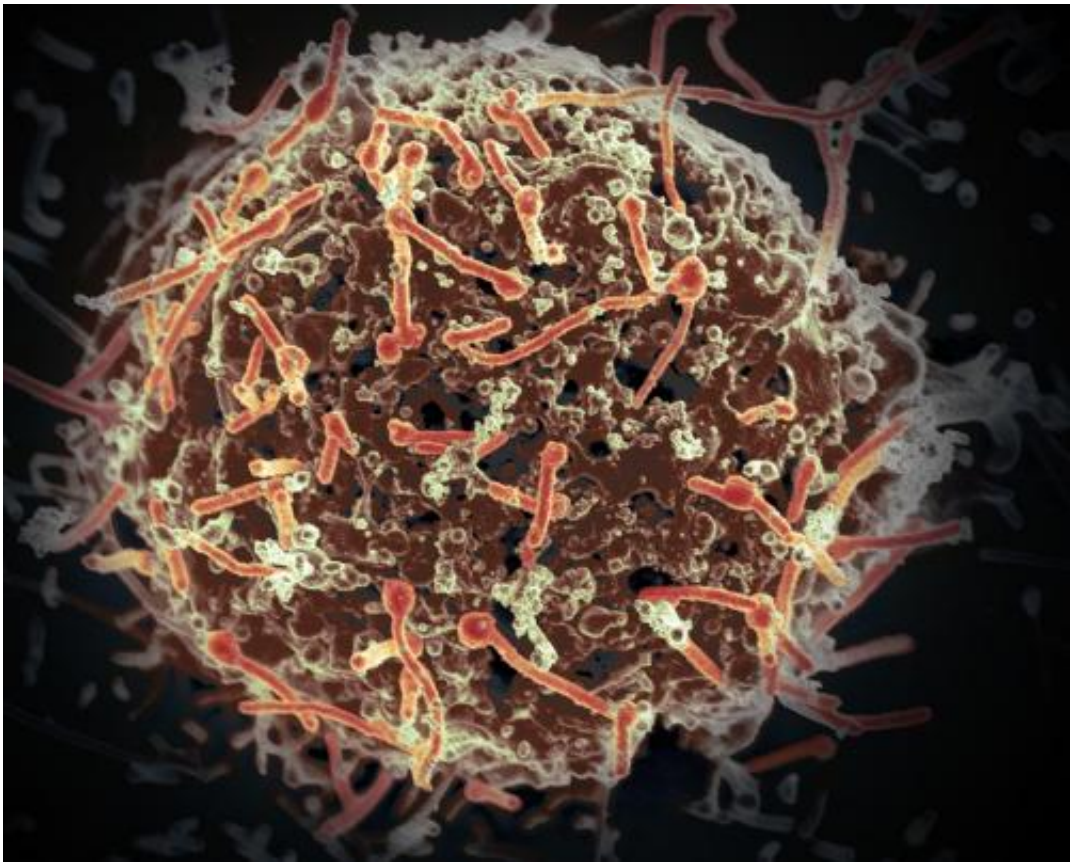

The Ebola virus, isolated in November 2014 from patient blood samples obtained in Mali. The virus was isolated on Vero cells in a BSL-4 suite at Rocky Mountain Laboratories. Credit: NIAID

In late December, nearly two years after the epidemic began, the World Health Organization has declared the African country of Guinea to be

free of Ebola virus infections. But, the race to find a cure and therapies to combat the disease are forging ahead as officials warn that inattention could lead to another epidemic.

Texas Biomedical Research Institute scientists have been working on therapies, diagnostics and vaccines for years before the 2014 epidemic, and a recent study by Dr. Anthony Griffiths to be published in the *Journal of Virology* shows a promising mechanism for attacking the virus. The paper will be in Issue 5 March 2016 print edition but is already available online.

In the paper, titled Determination and Therapeutic Exploitation of Ebola Virus Spontaneous Mutation Frequency, Dr. Griffiths explains how "typically, RNA viruses have high spontaneous mutation rates, which permit rapid evolution and the ability to adapt to new selection pressures. These selection pressures can include antiviral drugs, the immune system, or even new animal hosts." However, it was unknown whether filoviruses exhibit high mutation frequencies.

"When we started this work, there was not an appreciation that Ebola virus had any capacity to evolve and if those changes would be well tolerated," Griffiths explained.

Griffiths and his team, that included graduate student Kendra Alfson, used ultra deep sequencing to reveal that the spontaneous mutation frequency for Ebola virus was high and similar to other RNA viruses. However, "We found that Ebola virus had very limited ability to tolerate spontaneous changes in the genome, thus it was reasoned that chemically increasing the mutation frequency may decrease the number of viable virions released from a cell."

Essentially, Ebola virus has the potential to evolve rapidly but the genetic changes result in viruses that are weakened or not viable. Due to the

unprecedented numbers of individuals infected in the latest outbreak, we have learned that Ebola virus does evolve in humans. Therefore, a better understanding of the capacity of the virus to evolve could lead to better diagnostics and potential therapies.

"Any change in a genome can be neutral, negative, or positive to a virus," Griffiths explained. He added that "interestingly, viruses appear to have evolved to have an optimal mutation rate. Increasing the mutation rate could produce a negative effect on the virus and serve as a valuable therapeutic tool."

To determine whether Ebola virus was sensitive to increasing mutation rate, Griffiths' group tested a drug called ribavirin.

Preliminary experiments with mice suggested ribavirin could be a potential therapy and did cause the desired effect of increasing the mutation frequency enough to make the virus non-viable. Further testing in monkeys showed ribavirin reduced production of infectious Ebola virus but results were not strong enough to recommend ribavirin as a treatment protocol.

"Now we have shown the potential of modifying mutation rate as a therapeutic tool for Ebola virus infections," Griffiths said. "We plan to test other drugs in the hope of improving the efficacy observed using ribavirin."

More information: Kendra J. Alfson et al. Determination of the Spontaneous Mutation Frequency of Ebola virus and Exploitation of this Therapeutically, *Journal of Virology* (2015). DOI: 10.1128/JVI.02701-15

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