Genetic changes in Ebola virus in West African outbreak could hinder potential treatments

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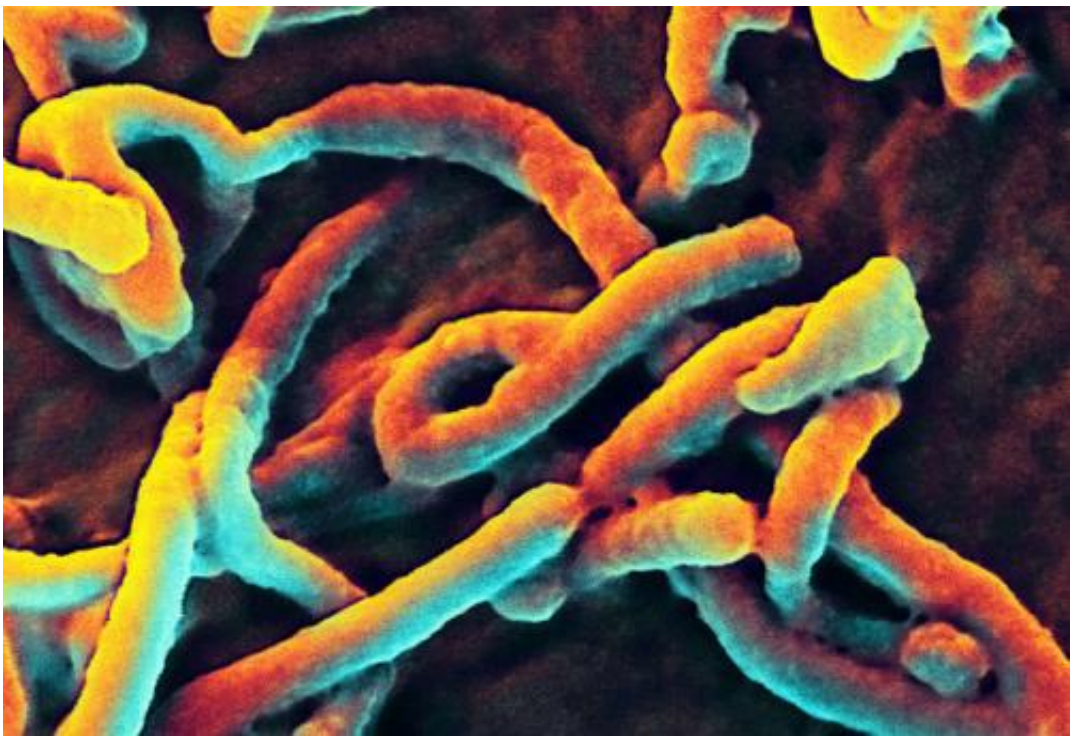

A scanning electron micrograph of Ebola virus budding from a cell (African green monkey kidney epithelial cell line). Credit: NIAID

Researchers have tracked the genetic mutations that have occurred in the Ebola virus during the last four decades. Their findings, published in *mBio*, the online open-access journal of the American Society for Microbiology, identified changes in the current West African outbreak

strain that could potentially interfere with experimental, sequence-based therapeutics.

"We wanted to highlight an area where genomic drift, the natural process of evolution on this RNA virus genome, could affect the development of therapeutic countermeasures," says Gustavo Palacios, senior author of the study and director of the Center for Genome Sciences at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Frederick, Maryland.

Many of the most promising drugs being developed to fight Ebola are therapeutics that bind to and target a piece of the virus's genetic sequence or a protein sequence derived from that genetic sequence. If that sequence changes due to genetic drift, the natural evolution of the virus over time, then the drugs may not work effectively.

"Our work highlights the genetic changes that could affect these sequence-based drugs that were originally designed in the early 2000's based on virus strains from outbreaks in 1976 and 1995," says Palacios.

The team compared the entire genomic sequence of the current outbreak strain, called EBOV/Mak, with two other Ebola virus variants—one from an outbreak in Yambuku, Zaire (now the Democratic Republic of the Congo) in 1976 called EBOV/Yam-May, and one from an outbreak in Kikwit, Zaire in 1995 called EBOV/Kik-9510621. They found changes, called single nucleotide polymorphisms, or SNPs, in more than 600 spots, or about 3% of the genome.

The sequence-based drugs currently offer the best hope for future treatment of Ebola outbreaks, but have not yet been approved by the US Food and Drug Administration or any other regulatory agency. Because the World Health Organization adopted emergency containment measures for the ongoing West African outbreak, these drugs are

currently being used to treat a few handfuls of patients in experimental testing. A clinical trial for one of the therapies will begin in Sierra Leone in the coming months.

The team, which included researchers from USAMRIID and Harvard University and the Massachusetts Institute of Technology, both in Cambridge, Massachusetts, then narrowed their search to only those mutations that changed the genetic sequences targeted by the various drugs. Of those, they found 10 new mutations that might interfere with the actions of monoclonal antibody, siRNA (small-interfering RNA), or PMO (phosphorodiamidate morpholino oligomer) drugs currently being tested.

The authors conclude that drug developers should check whether these mutations affect the efficacy of the therapeutic drug.

"The virus has not only changed since these therapies were designed, but it's continuing to change," says US Army Captain Jeffrey Kugelman, lead author and a viral geneticist at USAMRIID. Three of the mutations the team found appeared during the ongoing West African epidemic. "Ebola researchers need to assess drug efficacy in a timely manner to make sure that valuable resources are not spent developing therapies that no longer work."

Kugelman is currently in Charlesville, Liberia at the Liberian Institute for Biomedical Research, working with the local government to set up onsite genomics sequencing of Ebola patient samples to get a real-time picture of how the virus changes as it is transmitted from human to human. He'll be analyzing whether the virus's genetic sequences that are key for diagnostic tests and drug interventions change over time. "The virus mutates rapidly and it's an ongoing concern."