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Genetic Changes in Ebola Virus Could Impede Potential Treatments

Scientists studying the genetic makeup of the Ebola virus currently circulating in West Africa have identified several mutations that could have implications for developing effective drugs to fight the virus.

In today's online edition of the journal mBio, senior author Gustavo F. Palacios, Ph.D., and colleagues describe the "genomic drift," or natural evolution of the virus, and how it may interrupt the action of potential therapies designed to target the virus's genetic sequence.

According to Palacios, who directs the Center for Genome Sciences at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), three types of genetic sequence-based treatments are being evaluated during the current outbreak: monoclonal antibody, small-interfering RNA (siRNA), and phosphorodiamidate morpholino oligomer (PMO) drugs. All were developed using Ebola virus strains from two smaller outbreaks that occurred in 1976 and 1995.

Working with investigators from Harvard University and the Massachusetts Institute of Technology, the USAMRIID team compared the current strain, called EBOV/Mak, with the two previous strains that caused outbreaks in 1976 and 1995 in Zaire (now the Democratic Republic of the Congo). In each comparison, they found more than 600 genetic mutations. Next, the group focused on only the mutations that occurred in the genetic sequences targeted by the experimental therapeutics. Of these, they found 10 new mutations that might interfere with the mechanisms of the sequence-based drugs currently being tested. Three of these mutations appeared during the current West African outbreak.

The authors say genetic drift must be considered when developing potential therapeutics, in order to ensure that changes in the Ebola virus over time do not render those treatments ineffective.

Although none of the experimental drugs have been approved by the U.S. Food and Drug Administration, according to the investigators, they are being used to treat small numbers of patients under a World Health Organization (WHO) emergency protocol.

“Based on our findings, the virus has changed and is continuing to change,” said CPT Jeffrey Kugelman, Ph.D., the paper’s first author. Kugelman, a viral geneticist at USAMRIID, is currently working at the Liberian Institute for Biomedical Research, helping local officials to set up an onsite genomic sequencing capability for Ebola patient samples.

His work will be critical to analyzing changes in the virus’s genetic sequences over time and determining how those changes may affect future diagnostic tests and drug treatments.

USAMRIID’s mission is to provide leading edge medical capabilities to deter and defend against current and emerging biological threat agents. Research conducted at USAMRIID leads to medical solutions—vaccines, drugs, diagnostics, and information—that benefit both military personnel and civilians. The Institute plays a key role as the lead military medical research laboratory for the Defense Threat Reduction Agency’s Joint Science and Technology Office for Chemical and Biological Defense. USAMRIID is a subordinate laboratory of the U.S. Army Medical Research and Materiel Command.

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Reference: Kugelman JR, Sanchez-Lockhart M, Andersen KG, Gire S, Park DJ, Sealfon R, Lin AE, Wohl S, Sabeti PC, Kuhn JH, Palacios GF. 2014. Evaluation of the potential impact of Ebola virus genomic drift on the efficacy of sequence-based candidate therapeutics. mBio 6(1):e02227-14. doi:10.1128/mBio.02227-14.