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Venezuelan Equine Encephalitis Virus interacts with host cellular micro-RNA processing machinery to facilitate viral replication

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Venezuelan Equine Encephalitis Virus (VEEV) causes disease in both equine and humans that exhibit overt encephalitis in a significant percentage of cases. Despite being recognized as an emerging threat, relatively little is known about the virulence mechanisms of VEEV. Interference with critical host-pathogen interactions is an important area that can be utilized for therapeutic development. Recent publications implicate miRNA interactions in the pathogenesis of various viral diseases. While many viruses down-regulate the miRNA pathway to facilitate replication, some viruses such as Hepatitis C Virus utilize specific miRNAs and the RNAi machinery to enhance their replication. Based on this, we have begun to study miRNA processing in connection with VEEV replication. Our data indicate that knockdown of miRNA processing machinery significantly hinders VEEV replication. Loss of Drosha and DGCR8 had the greatest effect on VEEV production, indicating the need for nuclear processed miRNAs. In addition, siRNA knockdown of Ago2 decreased viral replication, which was confirmed with Ago2 null cells. Ago2 null cells also demonstrated significantly reduced VEEV capsid production and VEEV-GFP expression driven from the subgenomic promoter. These results were confirmed with a small molecule inhibitor of miRNA processing (ACF). Bioinformatic analysis indicated that five cellular miRNAs have complementarity to the VEEV subgenomic promoter. Anti-miRNA inhibitors to these 5 cellular miRNAs demonstrated that inhibition of miR-3683 reduced VEEV replication. Taken together, these findings indicate that loss of RNAi machinery severely limits VEEV replication and that specific cellular miRNAs contribute to VEEV replication.

Biography

Dr. Kylene Kehn-Hall received her Ph.D. in Biochemistry and Molecular Biology from The George Washington University studying retroviral pathogenesis and breast cancer biology. She did her post-doctoral research at the FBI Counterterrorism and Forensic Science Research Lab, focusing on assay development. In 2007 she took a Research Scientist position at USAMRIID, where she worked towards the identification of novel therapeutics for hemorrhagic fever viruses. Currently, she is a tenure-track Assistant Professor at the National Center for Biodefense and Infectious Diseases at George Mason University. Dr. Kehn-Hall's research is focused on the development of therapeutics for emerging infectious diseases, specifically Bunyaviruses, Alphaviruses, and HIV.

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