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Mohammad Mir

Western University of Health Sciences, USA

Hantavirus RdRp requires a host cell factor for Cap Snatching

The hantavirus RNA-dependent RNA polymerase (RdRp) snatches 5' capped mRNA fragments from the host cell transcripts and uses them as primers to initiate transcription and replication of the viral genome in the cytoplasm of infected cells. Hantavirus nucleocapsid protein (N protein) binds to the 5' caps of host cell mRNA and protects them from the attack of cellular decapping machinery. N protein rescues long capped mRNA fragments in cellular P bodies that are later processed by an unknown mechanism to generate 10- to 14-nucleotide-long capped RNA primers with a 3' G residue. Hantavirus RdRp has an N-terminal endonuclease domain and a C-terminal uncharacterized domain that harbors a binding site for the N protein. The purified endonuclease domain of RdRp nonspecifically degraded RNA *in vitro*. It is puzzling how such nonspecific endonuclease activity generates primers of appropriate length and specificity during cap snatching. We fused the N-terminal endonuclease domain with the C-terminal uncharacterized domain of the RdRp. The resulting NC mutant, with the assistance of N protein, generated capped primers of appropriate length and specificity from a test mRNA in cells. Bacterially expressed and purified NC mutant and N protein required further incubation with the lysates of human umbilical vein endothelial cells (HUVECs) for the specific endonucleolytic cleavage of a test mRNA to generate capped primers of appropriate length and defined 3' terminus *in vitro*. Our results suggest that an unknown host cell factor facilitates the interaction between N protein and NC mutant and brings the N protein-bound capped RNA fragments in close proximity to the endonuclease domain of the RdRp for specific cleavage at a precise length from the 5' cap. These studies provide critical insights into the cap-snatching mechanism of cytoplasmic viruses and have revealed potential new targets for their therapeutic intervention.

Biography

Mohammad Mir did his PhD from Saha Institute of Nuclear Physics, Department of Atomic Energy of India in 2003. He then Moved to University of New Mexico for his Postdoctoral training in Virology, where he worked with hemorrhagic fever viruses. He then joined the University of Kansas, School of Medicine as Assistant Professor in Virology in the year 2009. In 2015, he joined the Western University of Health Sciences, California, as Associate Professor in Virology. His research program at Western University is focused on replication and therapeutic intervention of emerging negative strand RNA viruses.

mmir@westernu.edu

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