Extended Abstract
Volume 4:1, 2020

Microbial Pathogenesis

Open Access

Crimean-Congo hemorrhagic fever virus nucleocapsid protein augments mRNA translation

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Abstract

Crimean-Congo hemorrhagic fever virus (CCHFV) is a tick-borne nairovirus of the Bunyaviridae family, causing severe illness with high mortality rates in humans. Here, we demonstrate that CCHFV nucleocapsid protein (CCHFV-NP) augments mRNA translation. CCHFV-NP binds to the viral mRNA 5' untranslated region (UTR) with high affinity. It facilitates the translation of reporter mRNA both in vivo and in vitro with the assistance of the viral mRNA 5' UTR. CCHFV-NP equally favors the translation of both capped and uncapped mRNAs, demonstrating the independence of this translation strategy on the 5' cap. Unlike the canonical host translation machinery, inhibition of eIF4F complex, an amalgam of three initiation factors, eIF4A, eIF4G, and eIF4E, by the chemical inhibitor 4E1RCat did not impact the CCHFV-NP-mediated translation mechanism. However, the proteolytic degradation of eIF4G alone by the human Rhinovirus 2A protease abrogated this translation strategy. Our results demonstrate that eIF4F complex formation is not required but eIF4G plays a critical role in this translation mechanism. Our results suggest that CCHFV has adopted a unique translation mechanism to facilitate the translation of viral mRNAs in the host cell cytoplasm where cellular transcripts are competing or the same translation apparatus.

The pure WT CCHFV N protein and stalk domain also detect vRNA panhandle of the Hazara virus, another Nairovirus in the Bunyaviridae family, indicating a specific type of N protein-panhandle interaction. Another RNA binding site was found in the primary CCHFV N protein domain that did not specifically specify single-strand RNA (ssRNA) of viral or non-viral origin. The description of the CCHFV N domain of the protein stalk that works to bind the panhandle, surprisingly inhibits the replication of the Hazara virus in cell cultures, demonstrating the role of protein-panhandle interactions in the replication of Nairovirus. Our findings present the stalk background of N protein as a target for therapeutic interventions to manage CCHFV disease.

This work is partly presented at 12th World Congress on Biotechnology and Microbiology