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Hantavirus induced cardiopulmonary syndrome: A public health concern

Hantavirus cardiopulmonary syndrome is characterized by pulmonary capillary leakage and alveolar flooding, resulting in 50% mortality due to fulminant hypoxic respiratory failure. In addition, depression of cardiac function ensues, which complicates the picture with cardiogenic shock. Early diagnosis and appropriate use of extracorporeal membrane oxygenation (ECMO) are amongst the lifesaving interventions in this fatal illness. Annually 150,000-200,000 cases of hantavirus infections are reported worldwide, and there is no treatment for this viral illness. There is an urgent need for the development of a vaccine and antiviral therapeutics to improve the prognosis of this deadly disease. The hantaviral genome is composed of three negative sense genomic RNA segments: S, M and L that encode nucleocapsid protein (N protein), glycoproteins (Gn and Gc) and viral RNA dependent RNA polymerase (RdRp), respectively. We showed that hantaviruses have evolved a novel translation initiation mechanism, operated by N protein, that preferentially favors the translation of viral mRNA in the infected host cell. N protein simultaneously binds to a highly conserved triplet repeat sequence of the viral mRNA 5' UTR and the 40S ribosomal subunit via the ribosomal protein S19 (RPS19). The simultaneous binding selectively loads the N protein associated ribosomes on viral transcripts and boosts their translation by avoiding the competition from host cell transcripts for the same translation apparatus. Using a high throughput screening assay we screened a chemical library of 100,000 chemical compounds to identify molecules that interrupt the N protein mediated translation strategy. Using this approach, we identified three lead inhibitors that selectively bind to N protein; inhibit N protein–UTR interaction and shutdown the N protein mediated translation strategy without affecting the canonical translation machinery of the host cell. The lead inhibitors are well tolerated by cells and their selective interruption in viral protein synthesis dramatically inhibits hantavirus replication. These inhibitors hold promise for the development of first anti-hantaviral therapeutic that will be of paramount importance in reducing disease mortality in hantavirus infected patients.

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.

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