Host Factor TUFM Differentially Associates with Viral Protein and Impedes Avian-like Influenza a Virus Replication in Human Cells

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Background/Objective
Influenza A viruses may evade species restrictions, cross species barriers, and further spread to humans with the potential to cause pandemics. Avian influenza A viruses typically do not efficiently replicate in mammalian cells. The substitution of glutamic acid (Glu, E) for lysine (Lys, K) at residue 627 of the polymerase basic protein 2 (PB2) of avian influenza viruses has been identified as a host-range and virulence determinant for mammalian infection. Although the PB2 627 variation is regarded as a species-specific signature of influenza A viruses, host factors associated with PB2 627 have yet to be fully investigated.

Method
Immunoprecipitation followed by differential proteomic analysis was performed to probe PB2 627K (human)- and PB2 627E (avian)-signature-associated proteins, and the results indicated that the elongation factor Tu, mitochondrial (TUFM) had a higher binding affinity for PB2 627E.

Result
Knocking down TUFM increased PB2 627E virus replication and restored viral mRNA synthesis, which was attenuated by PB2 K627E substitution in human cells. Conversely, the overexpression of TUFM decreased viral mRNA synthesis driven by PB2 627E-containing RNP. Similar finding was also observed with a stronger binding of TUFM to avian signatures PB2 590G/591Q and PB2 627E in the 2009 swine-origin pdmH1N1 and 2013 avian-origin H7N9 influenza A viruses.

Conclusion
Our results suggest that TUFM is a host restriction factor that is involved in PB2 627 adaptive mutations for avian influenza A viruses and impedes the replication of these viruses in human cells.