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Evolution of influenza A virus nucleoprotein is influenced by the E3 ubiquitin ligase activity of the interferon-inducible Tripartite Motif (TRIM)22 protein

Content

Influenza A virus (IAV) continuously mutates under both intrinsic and immunologically-driven selections. We previously identified TRIM22 protein as a restriction factor of seasonal but not of pandemic (pdm) H1N1 viruses. As TRIM22 restriction is due to a direct interaction with the viral nucleoprotein (NP) leading to its ubiquitination and proteasome degradation, we evaluated the evolution of NP lysine (K) residues that are target of TRIM22 E3 ubiquitin ligase activity from 1918 to 2009.

By sequence alignment, we identified four arginine (R) residues in NP of 1918 pdmH1N1 at position 98, 293, 422 and 446. These four R residues were progressively replaced by K residues in seasonal H1N1 strains since 1936 and were present from 1977 to 2009 when four R residues were reintroduced in the 2009 pdmH1N1. Single R-to-K or K-to-R mutations of pdm and seasonal NP, respectively, did not result in either gain or loss of TRIM22 restriction activity as measured in a viral polymerase activity assay. However, the combination of four R-to-K or K-to-R substitutions determined either a progressive gain or loss of TRIM22-dependent restriction, respectively. Introduction of four R into seasonal NP of H1N1 reconstructed by reverse genetics resulted in a loss of TRIM22 restriction concomitantly with a loss of NP ubiquitination by this restriction factor.

Our present findings indicate that TRIM22 is a component of an innate immunity barrier against zoonotic introduction of IAV in humans and suggests that adaptive mutations in NP should be carefully monitored as part of a surveillance effort to predict the potential occurrence of future pandemic IAV infections.

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