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Species comparisons identify avian ANP32A splice variants that differentially impact influenza A virus polymerase host restriction

Content

The viral RNA polymerase complex (vPol), comprising PB1, PB2 and PA, is essential for influenza A virus (IAV) replication. Cellular co-factors are necessary for vPol function, and host differences in these proteins act as barriers that limit IAV emergence into new species. ANP32A is a key host determinant of vPol efficiency that likely drives selection of mammalian-adaptive virulence motifs, such as PB2-627K: mammalian ANP32As lack a 33 amino-acid insert typically found in avian ANP32As, meaning they cannot support avian-motif (PB2-627E) IAV replication without viral adaptation. Here, we provide new insights into these selection mechanisms by functionally characterizing unique species' features of ANP32As from across the amniote clade of vertebrates. Surprisingly, our analyses suggest that inserts are a common component of both avian and crocodilian ANP32As, but that species-specific insert sequences restrict avian-signature vPol to using only the avian co-factor efficiently. We also uncovered that avian species express multiple ANP32A splice variants that differ only in insert sequence composition. Using deep sequencing, we found that chicken ANP32A harboring a 33 amino-acid insert is the predominant isoform normally expressed, but that minor insert variants with 29 or 0 amino-acids (mammalian-like, unable to enhance avian vPol activity) also exist. Strikingly, the 29 amino-acid insert lacks a hydrophobic SUMO-interaction motif (SIM)-like sequence that promotes vPol binding and is required for chicken ANP32A to fully support avian-signature IAV replication. We hypothesize that altered regulation of ANP32A splicing across species, tissues, or stress conditions could impact within-host IAV restriction and potentiation of pre-adaptation to non-avian co-factors.

Choose primary session

Viral Replication

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Virus host cell interaction

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