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Mx-mediated Host Restriction of Emerging Highly Pathogenic Avian Influenza H5N1 Viruses

Inhalt

Since 2022, H5N1 highly pathogenic avian influenza (HPAI) viruses of clade 2.3.4.4b caused unprecedented outbreaks in wild birds and increasing mammal infections, including spill-over into humans. These events raised concerns that H5N1 viruses may further adapt to humans. Indeed, some H5N1 viruses isolated from mammals carry adaptive mutations enhancing receptor binding and polymerase activity. However, efficient human-to-human transmission requires evasion of the human innate immune factor Mx1 (MxA), which restricts replication of zoonotic influenza A viruses (IAVs).

Here, we first investigated (i) if human MxA strongly suppresses H5N1 clade 2.3.4.4b viruses from mammals and (ii) when such H5N1 viruses can escape MxA restriction. Our results show that human MxA strongly suppresses replication of all tested H5N1 viruses *in vitro* and, to a lesser extent, in MxA-transgenic mice. Using a viral polymerase reconstitution assay, we found that replacing the H5N1 NP with that of a human-adapted H1N1 virus conferred MxA resistance. We further addressed reassortment potential of H5N1 with human-adapted IAVs carrying MxA-resistant NP segments. Using qPCR genotyping, we identified reassortants from co-infections and assessed their replication, polymerase activity and MxA evasion.

Our study reveals molecular barriers limiting transmission of zoonotic H5N1 and highlights genetic constellations possibly enhancing human adaptation, contributing to risk assessment and pandemic preparedness.

Keywords

Panzootic H5N1, Clade 2.3.4.4b, Mammalian adaptation, MxA restriction, Viral reassortment, Innate immunity, Pandemic risk assessment

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