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BTN3A3 resistance of emerging influenza A viruses is shaped by Mx1 of mammalian intermediate host species.

Inhalt

Zoonotic infections with influenza A viruses (IAVs) of animal-origin are typically self-limiting but can occasionally give rise to pandemics provided human host barriers are overcome. The recently identified human BTN3A3 (butyrophilin subfamily 3 member A3) is a potent restriction factor for zoonotic IAVs. Human-adapted IAVs overcome BTN3A3 restriction through adaptive residues 52 (N, H, Q) or 313 (Y, V) in the viral nucleoprotein (NP). Notably, these residues are associated with resistance to myxovirus resistance 1 (Mx1) proteins from human, swine, and bats. We thus hypothesized that BTN3A3 resistance might emerge as a result of Mx1-mediated selection pressure in intermediate hosts expressing antivirally active Mx1. To test this, we generated reassortant viruses carrying NP of different mammalian-derived IAVs and assessed viral replication in BTN3A3-expressing cells. Combining comparative mutagenesis with polymerase reconstitution assays, we found that NP residues conferring resistance to bat or swine Mx1 proteins also confer BTN3A3 resistance. Because bats and swine lack antivirally active BTN3A3, these adaptive residues emerged under Mx1-mediated selection pressure. Our findings demonstrate that resistance to the human restriction factor BTN3A3 can evolve in Mx1-competent intermediate hosts, providing new insight into the zoonotic potential of animal IAVs and the role of BTN3A3 in limiting zoonotic transmission.

Keywords

BTN3A3, influenza A virus, Mx1, zoonosis, host barriers

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21

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PhD student

Junior scientist status

Yes, I am a junior scientist.

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