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Reassortment between Avian and Human H3 Influenza Strains: Which Segments Co-Segregate with the Avian Virus Haemagglutinin?

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Reassortment of influenza A viruses is the underlying mechanism of antigenic shift resulting in emergence of pandemic strains with novel haemagglutinins (HA) which were transmitted from avian strains. However, the compatibility of the HA gene from such strains with the genes of a human acceptor virus has remained unclear. Here, we studied which genes of an avian strain co-segregate with its HA gene after co-infection with a human strain under forced selection for the heterologous HA. For that, we generated a strictly elastase-dependent HA cleavage-site mutant from A/Hongkong/1/68 (H3N2) (Hk68) via reverse genetics and performed co-infections of A549 cells with either A/Duck/Ukraine/1/63 (H3N8) (DkUkr63) or the more recent A/Mallard/Germany/Wv64-67/05 (H3N2) (MallGer05) in the absence of elastase but presence of trypsin to isolate reassortants carrying the avian virus HA exclusively. Both avian strains easily formed reassortants with the human virus carrying the avian HA with different gene constellations including those mimicking that of pandemic viruses with the DkUkr63 virus NA and/or PB1 segments. Overall, an elastase-dependent HA cleavage site mutant of a human strain as acceptor allows to assess the molecular correlates of gene segment compatibility and the ability of an avian strain to donate its HA segment to circulating human strains resulting in novel, antigenically shifted reassortants with pandemic potential.