Emerging Infections

543
The neuraminidase beside the Hemagglutinin is the essential virulence determinant of H5N1 high-pathogenic avian influenza viruses in chicken

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High-pathogenic avian influenza viruses (HPAIV) are restricted to the HA serotypes H5 or H7 and evolve from low-pathogenic precursors by acquisition of a polybasic HA cleavage site (HACS). However, previous introductions of such a polybasic HACS into several low-pathogenic avian strains with the serotypes H5N1, H3N8, H9N2, and H4N6 did not lead to high virulence in chicken and therefore revealed the presence of additional virulence determinants both in the HA and the other seven gene segments. To map those virulence determinants of HPAIV, we generated several reassortants from two H5N1 strains with widely differing virulence, the low-pathogenic A/Teal/Germany/Wv632/2005 (TG05) and the high-pathogenic A/Swan/Germany/R65/06 (R65), to investigate their pathogenicity in chicken. An R65 HA reassortant of TG05 displayed a lethality of 30% indicating that beside a polybasic HACS, the HA gene alone provides high virulence. Remarkably, additional replacement of the PB2, PB1, PA, and NP genes with those from R65 did not increase the lethality any further, indicating minor relevance of the polymerase complex for high virulence of HPAIV in the chicken host. However, a mirror-inverted reassortant composed of the TG05 polymerase and NP genes but the HA, NA, M and NS genes from R65 displayed 100% lethality. Further exchanges of the R65 gene segments revealed that the HA and NA alone enable 100% lethality (albeit at a prolonged median death time) and efficient transmission to contact chickens. Remarkably, a TG05 reassortant carrying the R65 HA, M and NS but the NA of TG05, showed reduced lethality of 30% like the R65 HA reassortant. Therefore, beside an HA with polybasic HACS, the NA is the second essential virulence determinant of HPAIV in chicken.

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