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The hemagglutinin, nucleoprotein and neuraminidase gene segments contribute to virulence in a chimeric H4/H5 avian influenza virus backgroundJ. Veits¹, J. Hundt¹, S. Weber¹, O. Stech¹, J. Stech¹, T. Mettenleiter¹

Friedrich-Loeffler-Institut, Molecular Biology, Greifswald-Insel Riems, Germany

Avian influenza viruses (AIV) possess segmented, negative-sense RNA genomes and belong to the family *Orthomyxoviridae*. Due to their virulence AIV are classified as low pathogenic (LP), exhibiting hemagglutinins (HA) of all known subtypes (H1-H16), or highly pathogenic (HP). HPAIV are restricted to the subtypes H5 and H7 with the main virulence determinant of a polybasic cleavage site (PCS) within the HA, which enables a proteolytic activation by ubiquitous proteases and in contrast to LPAIV are therefore capable to cause severe systemic disease in poultry. To investigate if this feature is sufficient to shift an LP to an HP phenotype in a non-H5/H7 background, we cloned A/mallard/Germany/1240/1/07 (H4N6) by reverse genetics with an artificial PCS (H4N6hp). However, the introduction of a PCS caused only a slight increase of virulence in infected chickens. Therefore, to investigate additional virulence determinants beside the PCS, we generated reassortant AIV of H4N6hp with all eight single gene segments of a H5N1 HPAIV exchanged. Reassortants exhibiting the H5N1 segments HA, neuraminidase (NA) and nucleoprotein (NP) showed increased virulence in chickens in the potency of HA, NP and NA. In concordance, reassortants with all possible combinations of these three segments in H4N6hp increased the virulence further on with lethal outcome. Therefore, besides the hemagglutinin and neuraminidase the nucleoprotein of H5N1 reveals a potent virulence determinant, at least in the given H4 genetic background.

Corresponding author:

Thomas Mettenleiter

thomas.mettenleiter@fli.bund.de