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Mechanisms of cold-adapted (CA) A/Krasnodar/101/35/59 (H2N2) influenza virus attenuation

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Comparative investigation of ts- and att- phenotype of single genic and polygenic reassortants between CA A/Krasnodar/101/35/59 (H2N2) influenza strain and virulent A/WSN/33 influenza strain obtained by the method of reverse genetics, testified that *PB1-gene* and *NS-gene* of CA strain contained the key determinants responsible for the ts phenotype and att-phenotype of this strain. To confirm this fact, ts-mutation in *PB1-gene* of CA strain was transferred into the genome of the virulent A/WSN/33 strain using site-specific mutagenesis. Obtained variant W9 purchased the ts-phenotype and was characterized by sharply reduced virulence for mice. On the other hand variant obtained by reversion of the mutation in PB1-gene of CA strain acquired the ability to reproduce at t 38°C and restored the virulence for mice upon intranasal infection. NS-gene of A/Krasnodar/101/35/59 strain contained the second key determinant responsible for the attenuation of this strain; however, had no mutational changes in its nucleotide sequence. The study of interferonogenic activity of reassortants derived between the CA strain and virulent A/WSN/33 strain showed that the ability to suppress the induction of interferon can be controlled by polymerase proteins of influenza virus (which coincides with the observations of Rei -Lin Kuo and R. Krug. 2009. The obtained data suggest that mutations in PA and NP proteins of CA strain leads to a destabilization of the NS-CPSF complex in infected cells. As a result A/Krasnodar/101/35/59 strain acquires the ability to induce interferon and loses virulent properties.

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