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Influence of pseudorabies virus pUS2 and pUL46 on ERK expression and integrity of the nuclear envelope

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Herpesviruses assemble capsids in the nucleus, while further maturation occurs in the cytosol. The efficient translocation from the nucleus to the cytosol is crucial for virus maturation. This step is mediated by envelopment at the inner nuclear membrane and deenvelopment after fusion with the outer nuclear membrane mediated by the nuclear egress complex (NEC), consisting of the conserved proteins designated in the alphaherpesviruses herpes simplex and pseudorabies virus (PrV) as pUL31 and pUL34. In the absence of either protein, virion formation is significantly impaired but not completely blocked. The residual infectivity of the deletion mutants was used for serial passaging in rabbit kidney cells. Wild type like titers were observed after several passages and replication competent viruses could be isolated. Ultrastructural analysis revealed that in these mutants NEC mediated translocation was bypassed by direct access of capsids to the cytosol through the fragmented nuclear envelope (Klupp et al., 2011). Sequencing of the genomes of the passaged mutants identified seven congruent mutations in coding regions, including tegument proteins pUL46 and pUS2 (Grimm et al., 2012). Both proteins have been shown to act on cellular signaling pathways. To test for involvement of these proteins in herpesvirus-induced nuclear envelope breakdown (NEBD), mutants were generated. While simultaneous deletion of pUS2 and pUL46 from wild-type PrV did not greatly impair viral replication and had no influence on nuclear envelope stability, deletion of pUL46 from either passaged mutant resulted in an enhanced NEBD. We are currently testing the effect of deletion of US2 and UL46 on ERK expression and whether this effect is related to NEBD.

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