1679. Interactions of the *Herpes Simplex Virus* γ34.5 Protein With Host Signaling Pathways Influence Central Nervous System Disease in Newborn Mice

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Background. Central nervous system (CNS) disease from HSV is a feared outcome of infection, and survivors often suffer lifelong neurologic sequelae. The HSV-1 protein γ34.5 is important for neurovirulence, counteracting the host type I interferon (IFN) response. Three distinct functions of γ34.5 have been reported, but their contributions to CNS disease have not been individually elucidated in different age groups.

Methods. We used mutant viruses and their corresponding revertants in models of HSV encephalitis to study the contribution of different functions of HSV γ34.5 to CNS disease in newborn and adult mice. Groups of mice, some with targeted mutations, were inoculated intracranially and followed over time for mortality. Viral replication in the CNS was assessed by plaque assay.

Results. Genetic deletion of the type I IFN receptor increases CNS virulence of wild-type (WT) HSV-1 in adult mice, leading to higher overall mortality, shorter time to mortality, and increased viral replication compared with WT hosts. In contrast, newborn mice had 100% mortality within four days of inoculation independent of the expression of the type I IFN receptor, with equivalent viral titers in the brains of both genotypes. Based on these results, we hypothesized that mutations of HSV-1 γ34.5 would retain virulence in this age group. Complete deletion of γ34.5 attenuated virulence in both adult and newborn WT mice, but virulence of this mutant remained distinct from its revertant virus in IFN receptor knockout mice, suggesting functions of γ34.5 other than affecting type I IFN are important. We have shown that the autophagy-inhibiting function of γ34.5 is dispensable for pathogenesis in newborn but not adult mice. In contrast, we show here that mutations in γ34.5 which disrupt the ability of HSV to counteract host translational shutoff via host PP1α, and mutations abrogating interaction with the host signaling protein TBK1, individually attenuate virulence in WT newborns.

Conclusion. The host translational shutoff and TBK1 functions of γ34.5 are important for HSV virulence in the CNS in newborn mice. Identification of factors important for HSV virulence in the CNS can identify therapeutic targets that may attenuate disease and serve as potential adjuvants to acyclovir.

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