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Varicella zoster virus tissue tropism and development of a neuroattenuated vaccine

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Abstract

Varicella zoster virus (VZV) infection causes chickenpox. After the primary infection, VZV remains latent in sensory ganglia, and reactivates upon weakening of the immune system, resulting shingles. The factors involved in neuronal invasion and establishment of latency are still elusive. In our previous work, we employed a VZV bacterial artificial chromosome system in order to characterize a comprehensive library of VZV open reading frame (ORF) deletion mutants. We reported 18 ORFs to be fully dispensable in melanoma cells. We postulated that the latter category is comprised of elements responsible for specific tissue tropism and, when removed, would yield a live neuroattenuated vaccine. By screening the 18 dispensable gene mutants in differentiated neurons, we found that ORF7 is a neurotropic factor adding to our previous report that ORF7 is also a skin tropic factor. ORF7 is a virion component localized to the Golgi compartment in infected cells, whose deletion causes loss of polykaryon formation *in vitro* and severely impairs viral spread in human nervous tissue *ex vivo*. Furthermore, we demonstrated that ORF7 is required for VZV replication in xenografts of human skin and dorsal root ganglia in a humanized mouse model. Now show that the ORF7 deletion virus is able to infect dendritic cells, which in turn can infect T cells. Since VZV lacking ORF7 cannot cause either the primary chickenpox or the secondary herpes zoster diseases, these discoveries facilitate the development of a neuroattenuated vaccine against chickenpox and shingles, and a possible vector for delivery of other antigens.