Varicella-zoster virus tissue tropisms and neuro attenuated vaccine development

Hua Zhu
Rutgers New Jersey Medical School, USA

Varicella zoster virus (VZV) infection causes two distinct, but related diseases: varicella (chickenpox) following primary infection and zoster (shingles) after reactivation of latent VZV. VZV reactivation causes serious neurological diseases such as, post herpetic neuralgia, myelitis, stroke and giant cell arteritis especially in the elderly. The factors involved in neuronal invasion and establishment of latency are still elusive. In our previous work, we employed a VZV BAC system in order to characterize a comprehensive library of VZV single ORF deletion mutants. We reported 18 ORFs to be fully dispensable in melanoma cells, which we postulated to encode elements responsible for specific tissue tropism. We now demonstrate that screening of these 18 dispensable gene mutants in differentiated neurons led to the identification of ORF7 as a neurotropic factor. This finding adds 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. Molecular mechanism of ORF7 in tissue tropism and pathogenesis are under investigation. Furthermore, ORF7 is required for VZV replication in xenografts of human skin and dorsal root ganglia in a SCID-hu mouse model. We showed that an ORF7 deletion virus is able to infect dendritic cells, which in turn can infect T cells. This unique set of characteristics lends an ORF7 deletion mutant the potential to become an excellent VZV vaccine candidate. This neuro attenuated vaccine would cause neither the primary chickenpox nor the secondary herpes zoster diseases. Finally, given that ORF7 is essential for VZV initial infection of neurons and replication therein, it may also be a critical trigger of reactivation from latency.

Biography
Hua Zhu has obtained his PhD degree from Columbia University and completed his Post-doctoral studies from Princeton University. He has been working on herpesviruses for over 20 years. He started with studying human cytomegalovirus (HCMV) immediate-early gene function. He performed pioneer works on global cellular transcriptional responses to viral infection using differential display and gene chip technology. One important discovery from these studies is how HCMV infection activates large numbers of interferon-stimulated genes. Later, he applied the bacterial artificial chromosome (BAC) technology to study HCMV and varicella zoster virus (VZV) gene function, tropism and pathogenesis. He is one of the first to construct for HCMV and VZV BACs. He also used humanized mouse model and luciferase assay to study viral replication in vivo. He was first to discover VZV neurotropic factor which leads to a novel neuro-attenuated VZV vaccine candidate developed. He has published over 70 research articles, reviews and book chapters.

zhuhu@njms.rutgers.edu