THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Chandra M. Menendez

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

Friday, April 21, 2017, 2:00 p.m.
Biomedical Research Center, Room 109, OUHSC

HSV-1 TARGETS THE BRAIN EPENDYMAL REGION DURING ACUTE ENCEPHALITIS WHICH PROMOTES VIRAL PERSISTANCE IN LATENTLY INFECTED MICE

COMMITTEE IN CHARGE: Daniel J.J. Carr, PhD, Chair, Lauren A. Zenewicz, PhD, Rodney K, Tweten, PhD, Paul Kincade, PhD, Michael Elliott, PhD

ABSTRACT: HSV-1 is a neurotropic pathogen that is transmitted by human contact and/or fomites where the virus will infect and replicate within epithelial cells of the facial mucosa (acute phase). Virions will lytically escape epithelial cells to invade innervating sensory neurons of the trigeminal ganglia (TG) where the virus establishes latency. HSV-1 can reactivate from this dormant state leading to manifestations of the periphery, such as cold sores and/or ocular keratitis. HSV-1 can also traffic into the central nervous system (CNS) and cause Herpes Simplex Encephalitis (HSE), a devastating disease that can result in mortality or long term neurological deficits. The mechanisms enabling virions to infect and promote potential long-term CNS pathology are poorly defined. Additionally, whether the CNS is a reservoir of viral latency post-infection remains enigmatic. Therefore, we rigorously characterized the susceptibility of specific CNS regions during the acute phase of infection and examined site-specific analysis as virus transitions into latency. Our results indicate that the brain ependymal region, composed of lateral ventricle ependymal cells and surrounding tissue, was associated with high viral titers and mortality of mice. At 30 days post infection (DPI), viral latency was assessed in the CNS and compared to the TG as a positive control. Strikingly, HSV-1 lytic gene transcripts, indicative of active viral replication, increased only in the ependymal region as the latent period of infection progressed (30 to 60 DPI). Successive detection of infected cells and HSV-1 antigen expression indicates that HSV-1 is actively replicating within the ependyma during latency. Resident memory T cells (T_{RM}) were sustained in number from 30 to 60 DPI, in the ependyma, yet they exhibited signs of exhaustion. In contrast, TG-localized T_{RM} decreased in number during latency, yet retained their effector capacity. In summary, we have described that the ependymal region of the CNS is highly susceptible during the acute phase of infection that leads to the subversion of latency in the form of viral persistence. Collectively, these data suggest that HSV-1 induces a persistent infection and inflammatory phenotype that putatively correlates with poor long-term neurologic performance in animal models and humans.