S7-2

Herpes Simplex Virus and Immunity

Chong-Kyo Lee
Korea Research Institute of Chemical Technology

Herpesviruses are a diverse group of large double-stranded DNA viruses that have a common virion structure with envelope. There are 8 members of human herpes viruses (HHV) and all of them establish latent infection which allow viral persistence to go largely unnoticed by the immune system. Herpes simplex virus (HSV) type 1 (HSV-1), HSV type 2 and varicella-zoster virus are HHVs and members of the alphaherpesvirinae subfamily. They are neurotropic and can infect nerve endings and be transported by retrograde zonal flow to neuronal nuclei where they can establish latency. They are avoid of recognition by the immune system because of the extremely limited gene expression. The immune system plays some role in curtailing viral spread in the nervous system during acute, primary infection and establishment of latency. But immune responses of the naïve body infected with HVS-1 are not well understood. Acquisition of primary HSV-1 infection usually occurs after contact with infected saliva or a person with oral lesions. Although most infections are asymptomatic, HSV-1 infections can cause gingivostomatitis, conjunctivitis, keratitis, and herpetic whitlow. HSV-1 infections are also responsible for more than 95% of HSV encephalitis cases.

Thymidine kinase (TK) HSV-1 is unique in that it possesses low substrate specificities and has the additional enzymatic activities of deoxycytidine kinase and TMP kinase. Much efforts have been focused on vTK, because of the roles of the viral TK in activation of many antiviral agents such acyclovir and ganciclovir, antiviral resistance, chemomodulation aimed at selectively killing genetically modified cancer cells with antiherpetic drugs. Although a lot of efforts have been made regarding viral replication and pathogenesis, such as virulence, establishment of latency and reactivation from latency, the in vivo functions of the HSV TK are not clearly understood.

Here I report that the HSV-1 TK was responsible for the evasion from viral clearance in virus-infected mice probably by escaping from innate immunity. Unlike Mice infected with the viral strain with TK-positive or TK-partial (little but still some) activity, TK-negative strains showed rapid clearlance of viruses in lungs (Fig. 1). This phenomenon was observed only in vivo. When lung were isolated and incubated in a 37°C CO_2 incubator under ex vivo conditions, there was no difference between TK-positive and the TK-negative strains (Fig. 2). The TK proteins were found in virions (Fig. 3), The TK proteins in virus particles may interact with host defense systems resulting in inhibition, interference or modulation of the host response to early infection. The viral TK may be a good tool to elucidate the early innate immune mechanisms.

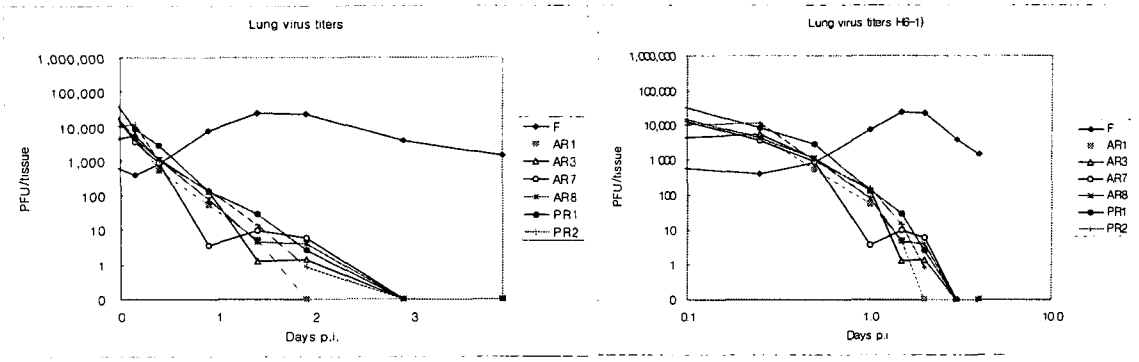


Fig. 1. Virus titers of lungs isolated from mice infected with HSV-1 intranasally
A) The wild type strain (F) and TK-negative strains (AR1, AR3, AR7, AR8, PR1, PR2)
B) The wild type strain (F) and TK-partial strains (AR2, AR4, AR5, AR6, AR9, PR1, PR2)

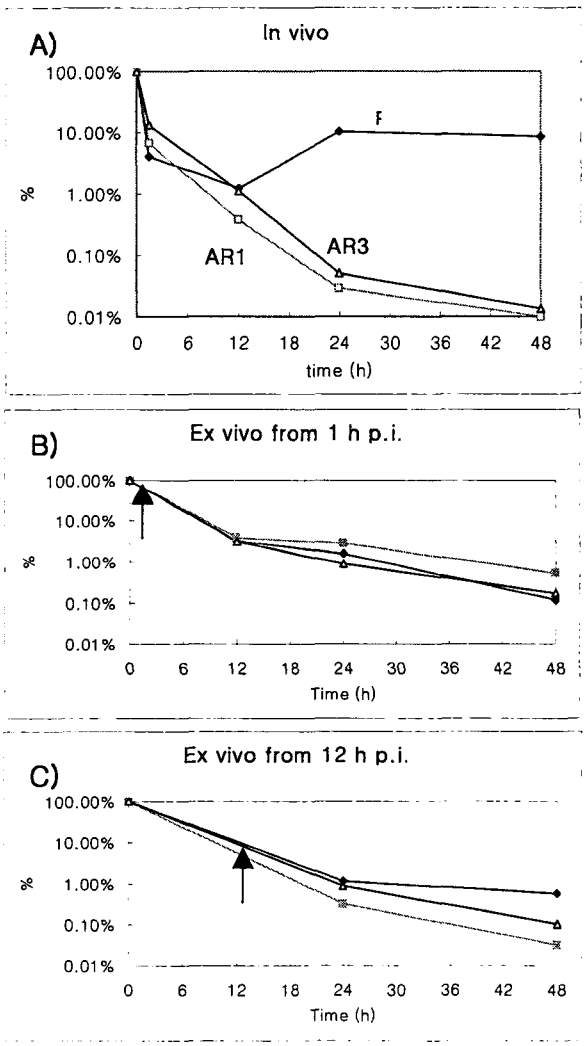
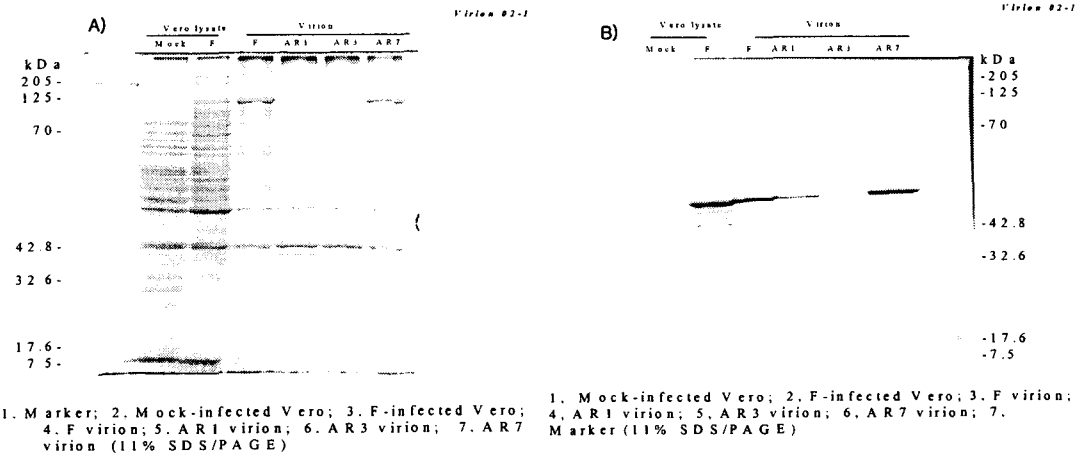


Fig. 2. Virus titers of lungs isolated from mice infected with HSV-1 intranasally
A) Lungs taken out from mice directly
B) Lungs were taken out from mice after 1 h p.i. and further incubated at 37°C CO_2 incubator
C) Lungs were taken out from mice after 12 h p.i. and further incubated at 37°C CO_2 incubator



1. Marker; 2. Mock-infected Vero; 3. F-infected Vero; 4. F virion; 5. AR1 virion; 6. AR3 virion; 7. AR7 virion (11% SDS/PAGE)

1. Mock-infected Vero; 2. F-infected Vero; 3. F virion; 4. AR1 virion; 5. AR3 virion; 6. AR7 virion; 7. Marker (11% SDS/PAGE)

Fig. 3. Purification of HSV-1 virions and Western analysis of viral TK proteins
A) Coomassie blue stain,
B) Western analysis probe with polyclonal rabbit anti-TK antibodies