Department of Virology

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General Summary

Human herpesvirus (HHV) is frequently reactivated and can establish a lifelong latent infection of its host. We are studying the molecular mechanism of latency and the pathogenesis of human cytomegalovirus and HHV-6, and have found a novel latent protein of HHV-6 which is associated with ~~and~~ mood disorders. We are also applying HHV-6 and HHV-7 as tools for studying the mechanism of fatigue. The salivary levels of HHV-6 and HHV-7 DNA increase with training and decrease with rest, suggesting their usefulness as biomarkers of physiological fatigue and cancer-related fatigue (CRF).

Research Activities

Attenuation of HHV-6B reactivation by aging

Objective: Little research has examined HHV-6B in healthy adults, and the prevalence of HHV-6B in different age groups is unclear. Therefore, this study evaluated the seroprevalence of anti-HHV-6 antibodies in office workers and examined the effect of aging on seroprevalence. Because HHV-6B is reactivated in saliva, this study also investigated the association of age and HHV-6B reactivation by measuring salivary HHV-6 DNA levels.
Methods: The subjects were 77 office workers who underwent a health checkup. Anti-HHV-6 antibody titers were measured via enzyme-linked immunosorbent assay and salivary HHV-6 DNA levels. Associations were examined with age and, as confounding factors, with body mass index, smoking habit, and alcohol consumption.
Results: The seropositivity of anti-HHV-6 antibodies was significantly decreased in subjects 50 years or older, and anti-HHV-6 antibody titers were negatively correlated with age. Salivary HHV-6 DNA levels were also negatively correlated with age but were not significantly correlated with other factors.
Conclusions: Our results suggest that HHV-6B reactivation is attenuated by aging. Thus, anti-HHV-6 antibodies steadily decrease in the body with aging.

Clinical significance of CRF in patients with multiple myeloma

An adverse event in patients who have multiple myeloma (MM) and are treated with cytotoxic agents, proteasome inhibitors, and immunomodulatory drugs, such as bortezomib, lenalidomide, and thalidomide, is CRF. This study prospectively analyzed the clinical significance of CRF and evaluated the cumulative incidence of CRF and the survival rates of 16 patients who had MM and were treated with proteasome inhibitors and immunomodulatory drugs. Reactivation of salivary HHV-6 and HHV-7 was analyzed with the real-time quantitative polymerase chain reaction. The incidence of CRF was evaluated with a visual analog scale. The subjects were 11 patients with newly diagnosed MM and 5 with relapsed or refractory MM. The cumulative incidence of CRF was 54.9% overall

but was not associated with the type of treatment. The cumulative incidence of reactivation was 73.1% for HHV-6 and 45.6%, for HHV-7. However, the reactivation of HHV-6 and HHV-7 was not related to CRF. The overall survival and progression-free survival in patients with newly diagnosed MM was significantly shorter for those with CRF than for those without CRF. In conclusion, CRF is a major symptom in patients with MM and predicts shorter overall survival and progression-free survival in patients with newly diagnosed MM.

Increased levels of interleukin 1β and basic fibroblast growth factor in cerebrospinal fluid during HHV-6B encephalitis

A member of the β herpesvirus subfamily is HHV-6, which is further subdivided into HHV-6A and HHV-6B. Exanthema subitum typically results in fever and rash but resolves spontaneously without further complications or illness. However, in rare cases, HHV-6B infection can lead to encephalitis and has major clinical implications. Immunodeficiency associated with clinical procedures, such as hematopoietic stem cell transplantation, has been reported as a factor in HHV-6B-induced encephalitis; however, in cases of primary HHV-6B infection without immunodeficiency, the factors responsible for disease onset remain elusive. Levels of interleukin (IL) 1β and basic fibroblast growth factor (bFGF) in cerebrospinal fluid were found to be higher in patients with HHV-6B encephalitis than in patients with non-HHV-6B-induced febrile seizures. In vitro expression of the HHV-6B gene in infected U373 astrocytes was enhanced by IL-1β during the initial phase of infection and by bFGF during the maintenance phase. These findings indicated that IL-1β and bFGF contribute to HHV-6B growth and the onset of encephalitis.

Publications

Kobayashi N, Nishiyama T, Yamauchi T, Shimada K, Suka M, Kondo K, Yanagisawa H. Attenuation of human herpesvirus 6B reactivation by aging. *J Med Virol.* 2019; **91:** 1335-41. Epub 2019 Feb 27.

Suzuki K, Kobayashi N, Ogasawara Y, Shimada T, Yahagi Y, Sugiyama K, Takahara S, Saito T, Minami J, Yokoyama H, Kamiyama Y, Katsube A, Kondo K, Yanagisawa H, Aiba K, Yano S. Clinical significance of cancer-related fatigue in multiple myeloma patients. *Int J Hematol.* 2018; **108:** 580-87.