Department of Virology

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General Summary

Human herpesvirus is capable of establishing a lifelong latent infection of their host, is reactivated frequently. We are studying the molecular mechanism of latency and pathogenesis of human cytomegalovirus (HCMV) and human herpesvirus 6 (HHV-6), and find a novel latent protein of HHV-6 which associate with and mood disorders. We are also trying to apply HHV-6 and HHV-7 to the tools for studying the mechanism of fatigue. Salivary HHV-6 and HHV-7 DNA amounts increased with training and decreased with rest, suggesting usefulness as biomarkers of physiological fatigue. Additionally we study on cognitive impairment and Alzheimer's disease which we have previously shown the relationship to fatigue and herpesvirus reactivation.

Research Activities

Increased interleukin-1β and basic fibroblast growth factor levels in the cerebrospinal fluid during human herpesvirus-6B (HHV-6B) encephalitis

Human herpesvirus (HHV)-6 is a member of the β herpesvirus subfamily. HHV-6 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. We detected higher levels of interleukin (IL)-1β and basic fibroblast growth factor (bFGF) in the cerebrospinal fluid (CFS) of patients with HHV-6B encephalitis when compared to those in patients with non-HHV-6B-induced febrile seizures. In vitro, IL-1β and bFGF enhanced HHV-6B gene expression in infected U373 astrocytes during the initial and maintenance phases of infection, respectively. These findings indicated that IL-1β and bFGF contribute to HHV-6B growth and the onset of encephalitis.

Usefulness of DNA Methylation Levels in COASY and SPINT1 Gene Promoter Regions as Biomarkers in Diagnosis of Alzheimer's Disease and Amnestic Mild Cognitive Impairment

In order to conduct early therapeutic interventions for Alzheimer's disease (AD), convenient, early diagnosis markers are required. We previously reported that changes in DNA methylation levels were associated with amnestic mild cognitive impairment (aMCI) and AD. As the results suggested changes in DNA methylation levels in the COASY and SPINT1 gene promoter regions, in the present study we examined DNA methylation in

these regions in normal controls (NCs, n = 30), aMCI subjects (n = 28) and AD subjects (n = 30) using methylation-sensitive high resolution melting (MS-HRM) analysis. The results indicated that DNA methylation in the two regions was significantly increased in AD and aMCI as compared to NCs ($P < 0.0001$, $P < 0.0001$, ANOVA). Further analysis suggested that DNA methylation in the COASY gene promoter region in particular could be a high sensitivity, high specificity diagnosis biomarker (COASY: sensitivity 96.6%, specificity 96.7%; SPINT1: sensitivity 63.8%, specificity 83.3%). DNA methylation in the COASY promoter region was associated with CDR Scale Sum of Boxes (CDR-SB), an indicator of dementia severity. In the SPINT1 promoter region, DNA methylation was negatively associated with age in NCs and elevated in aMCI and AD subjects positive for antibodies to Herpes simplex virus type 1 (HSV-1). These findings suggested that changes in DNA methylation in the COASY and SPINT1 promoter regions are influenced by various factors. In conclusion, DNA methylation levels in the COASY and SPINT1 promoter regions were considered to potentially be a convenient and useful biomarker for diagnosis of AD and aMCI.

Publications

Tamai M, Kobayashi N, Shimada K, Oka N, Takahashi M, Tanuma A, Tanemoto T, Namba H, Saito Y, Wada Y, Okamoto A, Ida H, Kondo K. Increased interleukin-1beta and basic fibroblast growth factor levels in the cerebrospinal fluid during human herpesvirus-6B (HHV-6B) encephalitis. *Biochem Biophys Res Commun.* 2017; **486:** 706-11.