Borna Disease Virus Infection and Its Role in Chronic Fatigue Syndrome

Neurobehavioral disorder is a serious consequence of a number of viral infections in the central nervous system (CNS). Borna disease virus (BDV) belongs to the *Bornaviridae* family, within the nonsegmented, negative-stranded RNA viruses, which is characterized by low productivity, neurotropism and nuclear localization of transcription and replication. Also, BDV shows noncytolytic replication in infected cells and therefore easily establishes persistent infection, which may be important for BDV-induced neuropathogenesis. Although BDV was originally described as an agent of nonpurulent encephalomyelitis in horses in Germany, BDV infection has now been found in a wide range of vertebrate species. Furthermore, recent epidemiological studies suggest that BDV infection also occurs in humans and that it may be related to certain human neurological diseases. Our studies on BDV epidemiology have shown that BDV prevalence is higher in patients with chronic fatigue syndrome (CFS) than in healthy controls.

To understand the linkage between BDV infection and CFS, as well as to elucidate the molecular nature of BDV neuropathogenesis, we developed several analysis systems using persistently BDV-infected cultured cells and experimental animals, such as rats and gerbils. In these experiments, we identified that a multifunctional protein, amphoterin (HMGB1), directly binds to a 24-kDa phosphoprotein (P) of BDV and that BDV infection or P expression in cultured neuronal cells can efficiently inhibit amphoterin functions, such as neurite outgrowth, cell migration and up-regulation of receptor for advanced glycation end products (RAGE). We also demonstrated that A-box region on amphoterin is responsible for the interaction with BDV P. Interestingly, the interference with amphoterin by BDV P modulated p53-mediated transcriptional activity, which is required a direct binding between amphoterin and p53 in the nucleus. Next, to understand the effects of amphoterin dysfunction in animal brains, we developed transgenic mice expressing BDV P in glial cells, as well as persistently BDV-infected neonate rat system. Glial expression of the transgene revealed a gradual deposit of the P in the CNS, especially at the neuropil in the hippocampus, without

astrocytosis and neuronal degeneration. Behavioral analyses of the transgenic mice showed enhanced intermale aggressiveness and impairment of spatial reference memory. We demonstrate that the transgenic brains exhibit a significant reduction in brain-derived neurotropic factor and serotonin receptor expression, as well as a marked decrease in synaptic density. Thus, glial deposition or accumulation of BDV P may induce deleterious effects on the synaptic formation in the CNS. On the other hand, the rats neonatally infected with BDV developed normally and were apparently normal at 2-month-old. However, the rats rapidly showed neurological dysfunctions, including paralysis of the hind legs, after the induction of brain stress by the injection of lipopolysaccharide, in along with apoptosis of neuronal cells around BDV-infected cells. These findings may be helpful for understanding the possible involvement of BDV infection in the CNS disorders in the CFS.

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