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Herpes Simplex Virus Linked to Alzheimer's Disease

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Herpes simplex virus (HSV) is a neurotropic double-stranded DNA virus which includes the HSV-1 and HSV-2 subtypes. HSV is composed of an inner DNA core, a capsid (e.g. VP22), the tegument, and an outer envelope, which is a lipid membrane containing glycoproteins. HSV-1 infects 60-80% of people worldwide and causes infectious corneal blindness, the common cold sore and potentially fatal encephalitis [1,2]. HSV is one of the leading infectious viral pathogens found in immunocompromised hosts, such as transplant recipients [3]. HSV induces tissue damage including cell infiltration, perivascular inflammation and syncytial formation [3]. HSV initially infects the epithelial cells and then enters the sensory nerve terminals. During its life cycle in the sensory nervous system, HSV travels by retrograde transport to the neuronal cell bodies in the trigeminal ganglia, and then either enters latency or replicates. Replicated or reactivated HSV travels by anterograde transport out of the cell body to the central nervous system in addition to the peripheral mucosal membrane.

Alzheimer's disease (AD) is a progressive neurodegenerative disease leading to the irreversible loss of neurons and the loss of intellectual abilities, including memory and cognition. According to the National Institute on Aging, AD afflicts 2.5-4.5 millions Americans and 18 million people worldwide. AD is pathologically characterized by intracellular neurofibrillary tangles and extracellular senile plaques. While the pathogenesis of AD is still elusive, it is widely recognized that APP plays a central role in the pathogenesis of AD based on the following evidence: i) APP is the precursor to beta-amyloid peptide (Abeta), a main constituent of senile plaques which causes cell death, synaptic defects and memory impairment [4-9]; ii) Disruption of APP-mediated axonal transport contributes to the neurodegeneration associated with AD [10]; iii) Aberrant APP phosphorylation results in Abeta production, cell stress and degeneration [10-12].

RT-PCR studies reveal the existence of HSV-1 DNA in plaques of frontal and temporal cortices in post-mortem brains of both sporadic and familial Alzheimer's disease [13-16]. The presence of HSV-1 in the brain is considered to be a risk factor for AD in elderly people who carry the apolipoprotein E ε4 allele [17]. Viral proteins of HSV-1 interact with many AD susceptibility genes or proteins [18]. In addition, epidemiological study demonstrates that HSV-1 reactivation, as measured by seropositive IgM, is a high risk factor for AD and that HSV-1 chronic infection contributes to the progressive brain damage characteristic of AD [19]. A more recent similar study shows that anti-HSV IgG antibody avidity is higher in AD patients and much higher in subjects with amnestic mild cognitive impairment (a prodromal stage of AD) than in controls, suggesting that seropositve IgG could be adopted as a biomarker for early diagnosis of amnestic mild cognitive impairment as well as AD [20]. These data suggest a link between HSV infection and AD pathogenesis. There have been numerous studies focused on deciphering the mechanisms behind this link.

A plethora of evidence shows that HSV-1 infection affects APP proteolytic processing, transport, phosphorylation and distribution [21-27]. A viral envelope glycoprotein B (gB) contains a sequence homologous to the carboxyl-terminal region of Abeta, a cleavage product of APP [21]. A peptide derived from gB accelerated the formation of Abeta fibrils which were toxic to primary cortical neurons [21]. Acute HSV-1 infection affects APP proteolytic processing both in vitro [21,22] and in vivo [23]. APP is co-isolated with HSV particles from HSV-1-infected Vero cells and isolated HSV-APP particles are able to transport in squid axon when injected into squid axon, suggesting a role of APP in mediating viral transport [25]. Further experiments in our lab have confirmed the co-localization of HSV-1 particles with APP inside cells under epifluorescent and electron microscopes [26]. A time-lapse live confocal imaging reveals that HSV-1 particles travel together with APP inside living cells [26]. This dynamic interaction between HSV-1 and APP results in pathological consequences: HSV-1 infection decreases the average velocity of APP vesicles and causes APP mal-distribution in infected cells [26].

Compromised transport and mis-localization of APP could contribute to increased APP proteolysis with HSV-1 infection [24], which may consequently cause cellular injury. In addition, HSV-1 infection of human neuronal cell line increases the phosphorylation of tau proteins, the main component of neurofibrillary tangles, one of the hallmarks of AD [28]. A viral kinase, UL13, which phosphorylates HSV-1 VP22, may phosphorylates human tau proteins [16]. Moreover, treatment of HSV-1-infected cells with acyclovir, the main antiviral agent used for treating HSV-1 infection by targeting viral DNA replication, substantially decreases the amount of Abeta and phosphorylated tau protein, two culprits of AD [29]. This finding not only supports the concept that HSV infection is involved in AD pathogenesis, but also opens up a novel window to slow or stop the progression of AD with antiviral strategies.

Collectively, HSV-1 infects a wide range of neurons and epithelial cells and transports bidirectionally in neurons and epithelial cells. HSV functions as intact functional machinery actively usurping a variety of cellular biological machineries by interacting with cellular proteins for its entry, transcription, DNA replication and egress. HSV infection and repeated reactivation result in the hyper phosphorylation of tau proteins as well as the disturbance of biogenesis, subcellular localization, phosphorylation and proteolytic processing of APP. Given the prevalent infection of HSV among people worldwide, the link of chronic HSV infection to AD and the potential use of HSV as a delivery vector for gene therapy, it is imperative to dissect the mechanisms for interaction between HSV and cellular proteins that are associated with AD. Clinical trials for evaluating the efficacy of antiviral drugs in the treatment of AD are urgently needed.

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