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Mini review

Herpes simplex virus type 1 persists in the aged brain through hypothetical expression of accessory genes

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Herpes simplex virus type 1 persists in the brain of most aged individuals and may contribute to the pathogenesis of Alzheimer's disease. The virus likely utilizes accessory genes for neural spread within the nervous system and herpes simplex virus type 1 may regulate various host responses through an array of accessory genes. This mini-review focuses on these viral accessory genes that may shed light on the potential mechanisms of this enigmatic phenomenon in the elderly brain. *Journal of NeuroVirology* (2010) **16,** 203–207.

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Introduction

Herpes simplex virus type 1 (HSV-1) is a ubiquitous neurotropic virus that infects humans. The virus establishes a lifelong latent infection in the peripheral nervous system (PNS), often in the trigeminal ganglia. Infected individuals usually remain asymptomatic, but the virus is periodically reactivated during stress and immunosuppression.

HSV-1 persists in the central nervous system (CNS), probably at a very low level, in aged individuals. Analyses using the polymerase chain reaction have detected HSV-1 DNA in the brain of most elderly people including Alzheimer's disease patients (reviewed in Itzhaki and Wozniak, 2008). Specifically, HSV-1 DNA has been detected within neurons (Mori *et al*, 2004; Wozniak *et al*, 2009a). There is evidence that the presence of HSV-1 in the brain is a risk factor for Alzheimer's disease in elderly people carrying the type 4 allele of the apolipoprotein E gene (Itzhaki *et al*, 1997).

Productive persistence

As immunosenescence progresses, HSV-1 likely performs a productive infection in the brain. HSV-1-specific immunoglobulin G (IgG) can be detected in the cerebrospinal fluid of most aged subjects (Wozniak *et al*, 2005). Mild forms of herpes simplex encephalitis may arise more frequently than expected (Klapper *et al*, 1984). Furthermore, spontaneous molecular reactivation, proposed in the PNS (Feldman *et al*, 2002), may occur in the CNS, where productive HSV-1 infection occurs in rare neurons in latently infected nervous tissue. Throughout infection, HSV-1 is actively controlled by immune surveillance (Hüfner *et al*, 2006; Knickelbein *et al*, 2008).

Accessory genes

The HSV-1 genome contains at least 74 distinct genes that can be classified into three groups according to their temporal expression: immediate-early (IE), early (E), and late (L) genes. These genes are also categorized into two groups based on whether they are required for viral replication in cultured cells. The 'essential genes' are critically required for replication *in vitro*. The 'accessory genes,' also known as 'nonessential genes,' are dispensable for replication *in vitro* and account for more than half of the HSV-1 genes (reviewed in Nishiyama, 2004). The latency-associated transcript (LAT) gene belongs to the latter category. HSV-1 requires such accessory genes to survive within humans and no HSV-1 mutants lacking even a single accessory gene have been isolated from humans.

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LAT

The ability of HSV-1 to establish and maintain a latent state in the PNS is largely due to the expression of LAT (reviewed in Mori and Nishiyama, 2006). LAT expression can block apoptosis, which enhances the survival of virus-containing neurons (Li *et al*, 2009). LAT-derived microRNAs may promote viral latency (Umbach *et al*, 2009). Two small RNAs encoded within the first 1.5 kb of the LAT gene may cooperatively block apoptosis (Shen *et al*, 2009). Interestingly, the LAT may stimulate the axonal regeneration (Hamza *et al*, 2007). Importantly, the LAT regulates IE gene expression by binding to the ICP0 (a promiscuous gene transactivator) and ICP4 (a transactivator of the E and L genes) genes. This regulation results in an overall decrease in viral protein production and, therefore allows the virus to evade the host immune responses. Additionally, the LAT locus regulates the expression of interferon (IFN) in neurons (Peng *et al*, 2005).

Expression of accessory genes in the CNS

Studies on experimental animal systems have shown that LAT can be expressed in the brain (Smith *et al*, 2000; Valyi-Nagy *et al*, 2000). However, it has been difficult to detect small amounts of HSV-1 RNA in human brain tissue (Steiner *et al*, 1994; Theil *et al*, 2004). As mentioned above, HSV-1 likely performs a productive infection, at least in a small number of infected neurons, where it synthesizes various accessory proteins.

Accessory proteins that promote neural spread

HSV-1 exhibits a frontotemporal distribution that can be explained by transmission through the trigeminal and olfactory routes (reviewed in Mori *et al*, 2005). Some accessory genes are likely involved in the viral spread within the nervous system (reviewed in Mori and Nishiyama, 2006). UL56 and US11 associate with kinesin, which contributes to anterograde axonal transport, whereas UL35 interacts with dynein, a protein that mediates retrograde transport. US7 (gI) and US8 (gE) are essential for the anterograde transport of HSV-1, and the latter mediates the retrograde transport (McGraw *et al*, 2009; McGraw and Friedman, 2009).

Accessory proteins that inhibit apoptosis

Apoptosis is a cellular mechanism that can remove virally infected cells from the host. Multiple accessories have been implicated in the regulation of apoptosis, including LAT, ICP4, ICP34.5, UL54, US1, US3, US5, and US6 (reviewed in Nishiyama, 2004). Among these potential antiapoptotic mediators, LAT (see above text) and US3 have been shown to inhibit apoptosis *in vivo*. US3 may block apoptosis by activating antiapoptotic substrates targeted by the cellular cyclic adenosine monophosphate (cAMP)-dependent protein kinase (Benetti and Roizman, 2004).

Accessory proteins that inhibit the host immunity

HSV-1 counteracts a variety of immune responses through accessory genes (Table 1). IFN is a powerful mediator of the innate immune responses in the CNS (reviewed in Conrady *et al*, 2009). IFN induces antiviral effector molecules, including double-stranded RNA-dependent protein kinase (PKR). PKR becomes activated upon binding to double-stranded RNA. Homodimers of active PKR phosphorylate eukaryotic initiation factor-2α (eIF-2α), resulting in translational arrest. US11 directly binds to PKR and inhibits its activity. And ICP34.5 forms a complex with the host protein phosphatase 1, thereby lifting the block on translation. Both US11 and ICP34.5 are required for full resistance to IFN (Mulvey *et al*, 2004). In addition, ICP0 and US3 may modulate toll-like receptor (TLR) responses.

Cellular immunity plays a significant role in immunological surveillance in the CNS (reviewed in Hickey, 2001). US12 interacts with the transporter associated with antigen processing (TAP), thereby blocking antigen presentation to cytotoxic T lymphocyte (CTL). ICP34.5 inhibits autophagy-mediated antigen presentation, and US3 and US5 attenuate the effector functions of CTL.

Accessory proteins that inhibit autophagy

Autophagy is an intracellular process that clears abnormal and/or excessive proteins and cellular organelles, as well as viruses. Activation of PKR and eIF2α plays a central role in cellular autophagic activity. ICP34.5 blocks PKR-dependent autophagic degradation of HSV-1 (Tallóczy *et al*, 2006). Moreover, ICP34.5 binds to the mammalian autophagy protein Beclin 1 and inhibits both autophagy function and autophagy-mediated antigen presentation (Orvedahl *et al*, 2007; Leib *et al*, 2009).

HSV-1 and amyloid-β

Amyloid-β (Aβ), a major component of the senile plaque, accumulates in the elderly brain

Table 1 HSV-1 accessory genes that can regulate host immune responses

Gene	Protein	Expression	Action target	Proposed mechanism
RL1	ICP34.5	L	IFN	Promotes the dephosphorylation of eIF-2α, thereby preventing the translational arrest (He *et al*, 1997)
			Antigen presentation	Regulates cell surface expression of class II molecules (Trgovcich *et al*, 2002)
			Antigen presentation	Interacts with Beclin 1, inhibiting autophagy-mediated antigen presentation (Leib *et al*, 2009)
RL2	ICP0	IE	IFN	Disperses promyelocytic leukemia protein from nuclear domain 10 structures (Chee *et al*, 2003)
			IFN	Inhibits IFN regulatory factor 3- and 7-mediated activation of IFN-stimulated genes (Lin *et al*, 2004)
			TLR	Recruits USP7 to inhibit TLR response (Daubeuf *et al*, 2009)
LAT			IFN	Interferes with and delays the expression of IFNs in neurons (Peng *et al*, 2005)
UL41	vhs	L	mRNA	Degrades mRNAs (for immune molecules such as IFN) by its endonuclease activity (Taddeo *et al*, 2006)
UL44	gC	L	Complement	Binds C3b to block the binding of C5 and properdin to C3b (Lubinski *et al*, 2002)
US3	US3	E	CTL	Blocks the cleavage of Bid by granzyme B (Cartier *et al*, 2003)
			CTL	Transmits a functionally inhibiting signal to CTL (Sloan *et al*, 2003)
			TLR	Interferes with TLR3-signaling (Peri *et al*, 2008)
US5	gJ	L	CTL	Protects target cells from granzyme B- and Fas ligand-mediated apoptosis (Jerome *et al*, 2001)
US8	gE	L	Antibody	Binds to the Fc domain of IgG, which blocks C1q binding to IgG and ADCC (Lubinski *et al*, 2002)
US11	US11	L	IFN	Associates with PKR and blocks its dsRNA-mediated activation (Cassady and Gross, 2002)
US12	ICP47	IE	Antigen presentation	Interacts with TAP and blocks peptide binding to TAP (Tomazin *et al*, 1996)

(Wasling *et al*, 2009). The internal amino acid sequence of HSV-1 gB is homologous to the carboxyl-terminal region of the Aβ peptide, and gB has been shown to initiate and promote Aβ fibril formation (Cribbs *et al*, 2000). HSV-1 infection upregulates enzymes responsible for Aβ-production and abnormal phosphorylation of tau (Wozniak *et al*, 2007, 2009b). The ICP34.5-mediated disruption of autophagy will lead to the further accumulation of Aβ (reviewed in Itzhaki *et al*, 2008). In turn, Aβ fibrils have been shown to stimulate HSV-1 infection (Wojtowicz *et al*, 2002). These observations suggest that there are molecular interactions between HSV-1 and Aβ in the human brain (Mori *et al*, 2004; reviewed in Itzhaki and Wozniak, 2008).

Simplified hypothesis

First, as immunosenescence progresses, HSV-1 that persists in the trigeminal ganglion and/or olfactory structures travels to the temporal and frontal cortices using accessory proteins. Second, HSV-1 counteracts an array of host responses in the CNS by expressing LAT and other accessory proteins. Third, HSV-1 initiates and enhances neuropathology encompassing Aβ-deposition, further enhancing the survival of the virus in the human brain.

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