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REVIEW

Control of HSV-1 latency in human trigeminal ganglia—current overview

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Abstract Although recurrent Herpes simplex virus type 1 (HSV-1) infections are quite common in humans, little is known about the exact molecular mechanisms involved in latency and reactivation of the virus from its stronghold, the trigeminal ganglion. After primary infection, HSV-1 establishes latency in sensory neurons, a state that lasts for the life of the host. Reactivation of the virus leads to recurrent disease, ranging from relatively harmless cold sores to ocular herpes. If herpes encephalitis—often a devastating disease—is also caused by reactivation or a new infection, is still a matter of debate. It is widely accepted that $CD8^+$ T cells as well as host cellular factors play a crucial role in maintaining latency. At least in the animal model, IFNγ and Granzyme B secretion of T cells were shown to be important for control of viral latency. Furthermore, the virus itself expresses factors that regulate its own latency–reactivation cycle. In this regard, the latency associated transcript, immediate–early proteins, and viral miRNAs seem to be the key players that control latency and reactivation on the viral side. This review focuses on HSV-1 latency in humans in the light of mechanisms learned from animal models.

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Introduction

Herpes simplex virus type 1 (HSV-1) is a large, double-stranded DNA virus which encodes for more than 80 proteins. Primary infection in humans usually occurs in the oral cavity during childhood. There, the virus replicates within the epithelial cells and undergoes its typical lytic life cycle with successive production of immediate early (IE), early, and late genes followed by production of infectious virions and lysis of the host cell.

Eventually, sensory nerve fibers feeding the site of inoculation, usually sensory neurons belonging to the maxillary and mandibular branch of the trigeminal ganglion (TG), are infected with the virus which then travels to the cell body of the neurons via retrograde transport. There, HSV-1 establishes lifelong latency (Baringer and Swoveland 1973), a state characterized by the existence of a functional viral genome without the production of infectious virus. During this time, the latency-associated transcripts (LATs) (Stevens et al. 1987) are the only prominent transcripts. It is still a matter of debate, if functional peptides or proteins originate from this transcript (Henderson et al. 2009). In latently HSV-1-infected TG, an abundant infiltration of cytokine- and chemokine-producing T cells is present (Theil et al. 2003a), most of them belonging to the $CD8^+$ compartment. Latency is believed to be controlled by LAT, infiltrating $CD8^+$ T cells and cellular control factors. Upon spontaneous reactivation, caused by different triggers like diseases, stress, and exposure to bright sunlight, the virus travels back to the peripheral tissue via anterograde transport, where it causes recurrent disease or asymptomatic shedding of the

virus. The mechanisms of axonal transport of HSV-1 are the subject of extensive research (Diefenbach et al. 2008; Huang et al. 2010; Antinone et al. 2010).

The difficulties in the investigation of HSV-1 infections in humans lie in the neuronal cell-tropism of HSV-1. Neuronal tissue is not accessed easily and thus can only be obtained from cadavers. Therefore, most of the facts we know about HSV-1 latency are derived from small animal models of infection, most commonly, the mouse. This is a useful tool, as different virus and animal strains can be studied and the host as well as the virus can be genetically engineered. Specific genes can be deleted or altered, and the effect on lytic and latent infection as well as reactivation can be studied in vivo and ex vivo. However, to actually infect mice, very high titers of HSV-1 are needed and HSV-1 is usually not spontaneously reactivating as it does in humans. As opposed to mice, in humans, co-infection with other viruses like the α-herpesviruses HSV-2 and varicella-zoster virus (VZV) is a common observation (Theil et al. 2003b). Also, as HSV-1 is highly adapted to its human host, co-evolution of host and virus cannot be studied in the mouse model. Therefore, it is an important matter to investigate whether observations made in animal models are mirrored in HSV's natural host.

Primary infection and establishment of latency

After a period of lytic replication in epithelial cells, HSV-1 enters the endings of sensory neurons and travels via retrograde transport to the sensory ganglia. In the mouse model, it is known that the arrival of the virus in the TG is followed by a short phase of increase in virus titers during which infectious virus can be detected in the TG (Liu et al. 1996). It is not clear if transfer of virus occurs from neuron to neuron or if multiple neurons become infected. As latent virus is only detected in the division of the TG where the respective innervating nerves from the site of infection project (Hüfner et al. 2009), it can be assumed that free viral particles are not abundantly produced in the human TG.

It is important to the host to control the initial replication of the virus, as it has been shown that there is a positive correlation between the extent of viral replication, the amount of latent genomes in the ganglia, and reactivation frequency (Thompson and Sawtell 2000; Sawtell et al. 1998; Sawtell 1998). An important role in controlling initial replication has been attributed to the innate immune system. Major viral replication in the TG occurs within days 3 to 5 after infection when adaptive immune responses are still developing. The initial immune infiltration in the TG consists of macrophages, natural killer cells, and γδ T cells (Liu et al. 1996; Shimeld et al. 1995). Later, from day 7 and on, the immune infiltrate is predominated by CD8, Mac-1, and tumor necrosis factor (TNF)-expressing cells (Liu et al. 1996) and expression of TNF-α, IFN-γ, IL-10, and CCL5 can be measured (Halford et al. 1996). Infiltration of $CD8^+$ T cells is concurrent with elimination of viral replication, and depletion of $CD8^+$ T cells leads to impairment of viral clearance (Simmons and Tscharke 1992). In humans, nothing is known about the events during early viral replication in the TG upon primary infection. As usually no sensory deficit is associated with primary infection, it might be assumed that neurons are either not killed by replicating virus or that viral replication does not occur. Also, in mice, apoptosis of neurons during initial infection is not observed (Esaki et al. 2010).

Establishment of viral latency seems to be quite independent from the immune system, since HSV-1 can establish latency in TG of mice lacking an innate and adaptive immune system (Ellison et al. 2000). Viral DNA entering the nucleus of its host cell immediately circularizes and associates with histones. In unstressed neurons, HCF1, which is needed for induction of viral IE-gene expression by VP16, is present in the cytoplasm, but not in the nucleus like in non-neuronal cells. In the absence of the VP16/HCF1/Oct1 complex, the viral genome remains associated with histones and the HDAC/CoREST/LSD1/REST repressor complex blocks activation of ß-genes. The viral genome is thereby silenced (Roizman 2011). There is no evidence that establishment of latency is actively regulated by the virus itself as no viral gene product is required (Wagner and Bloom 1997). Hence, latent infection seems to be the result of failure to enter the lytic cascade.

HSV-1 latency

Localization of latent HSV

Around 52% to 84% of the human population is latently infected by HSV-1 (Pebody et al. 2004). Persistence and latency have been demonstrated in human TG, facial ganglia, vestibular ganglia, geniculate ganglia, and the brain (Croen et al. 1987; Furuta et al. 1992, 1993; Theil et al. 2001, 2002; Hüfner et al. 2007; Verjans et al. 2007; Arbusow et al. 2010; Sanders et al. 1996). Nevertheless, the main site of latency and reactivation in humans seems to be the TG. It has been shown that the serostatus of infected individual correlates with occurrence of HSV-1 in the TG (Croen et al. 1987; Verjans et al. 2007). LAT is abundantly expressed in maxillary and mandibular divisions of the TG but almost absent in the ophthalmic division (Hüfner et al. 2009). This indicates that the virus infects neurons by entering axons that innervate the oral mucosa rather than by entering neurons in the TG.

In situ hybridization for LAT and also HSV-1 DNA revealed that neuronal nuclei are the major site of HSV-1 latency (Stevens and Cook 1971; Baringer and Swoveland 1973; Cook et al. 1974; Theil et al. 2003a, b). The number of infected neurons per human TG ranges from 1.3% (Held et al. 2011) to 3% (Cai et al. 2002), with most neurons containing less than 20 copies of the viral genome (Cai et al. 2002; Wang et al. 2005a; Held et al. 2011). Recently, it has been demonstrated in mice that HSV-1 preferably establishes latency in A5+ neurons whereas HSV-2 prefers KH10+ neurons (Margolis et al. 2007b; Imai et al. 2009). This finding has not been reproduced in human TG so far.

Viral transcription

Latency of HSV-1 is defined as retention of a functional viral genome without production of viral particles. During this latency period, viral transcription is basically limited to the LATs. It was long believed that, besides the LATs, there is no viral transcription during latency. As no protein had been associated with the 2-kb LAT, the major gene product during latency, HSV-1, was considered to hide from the immune system by limiting its gene expression. However, more recent studies showed minimal expression of other viral genes than LAT. Viral transcripts were identified in latently infected human (Derfuss et al. 2007; Held et al. 2011) and mouse TG (Kramer and Coen 1995; Chen et al. 1997, 2002a (197/id); Feldman et al. 2002). Even viral protein was detected in mice (Feldman et al. 2002; Sawtell 2003; Margolis et al. 2007a). In humans, only immediate early transcripts (ICP0 and ICP4) were detected whereas late proteins could only be found in productively infected brains of herpes encephalitis cases. In mouse TG, late proteins could also be identified (Feldman et al. 2002; Sawtell 2003; Margolis et al. 2007a).

Control of latency by the immune system

It is commonly known that immunosuppression leads to reactivation and severe HSV infections in humans (Montgomerie et al. 1969; Naraqi et al. 1977). Stress, known to be a stimulus for HSV-1 reactivation, was shown to induce immunosuppression (Pereira et al. 2003; revieved in Sainz et al. 2001). Also, in mice, psychological stress by disruption of social hierarchy within mouse colonies (Padgett et al. 1998) or restraint (Bonneau 1996; Freeman et al. 2007) caused immunosuppression and induced reactivation.

The effects of immunosuppression on reactivation and disease severity imply a role of the immune system in control of HSV-1. Actually, a persisting immune cell infiltration accompanied by cytokines and chemokines has been shown to occur in latently HSV-1-infected sensory ganglia in mice (Shimeld et al. 1995; Cantin et al. 1995; Halford et al. 1996) and also in humans (Theil et al. 2003a).

Characterization of immune infiltrates in the TG

Characterization of human TG infiltrates is mostly done by descriptive immunohistochemical studies at time of death of the host. Immune infiltrates in latently HSV-1-infected human TG have been characterized to consist primarily of $CD3^+$ T cells belonging to the $CD8^+$ subset as well as some $CD68^+$ macrophages. Only few $CD4^+$ T cells can be found surrounding neuronal cell bodies; most $CD4^+$ T cells are spread among the axons. In TG not infected with HSV-1, only scattered $CD3^+$ T cells can be found (Theil et al. 2003a). Derfuss et al. (2007) have shown that the majority of infiltrating T cells possesses an effector memory phenotype as they express CCR5 and CXCR3 as well as the corresponding ligands CCL5 and CXCL10. These receptors and their ligands are important for migration of T cells into the CNS and are known to be expressed on memory effector $CD8^+$ T cells. In addition, the voltage-gated potassium channel KV1.3 was expressed on many infiltrating T cells. The late effector memory phenotype of the $CD8^+$ T cell infiltrates in human TG has also been described by Verjans et al. (2007). Many $CD8^+$ T cells were positive for CD69, a marker for recent activation. Further characterization of surface molecules by fluorescence activated cell sorting of isolated T cells showed that TG resident $CD8^+$ T cells are $CD45RA^-RO^+$ $CD28^-CD27^-$. Naïve T cells express CD45RA, which is downregulated after Ag contact when T cells become CD45RO-positive. CD28 and CD27 are co-stimulatory molecules that are downregulated after antigen stimulation. Furthermore, no expression of lymph node homing receptors CCR7 and CD62L could be found. These features indicate recent activation of the T cells by antigens.

In the mouse model of latent HSV-1 infection, expression of Granzyme B is thought to be a marker for HSV-1 specificity and ongoing activation by the chronic stimulation of T cells in latently infected mouse TG (van Lint et al. 2005). Expression of Granzyme B in human TG infiltrating T cells has been shown on a subset of $CD8^+$ T cells (Derfuss et al. 2007; Verjans et al. 2007). Although most $CD8^+$ T cells present in the TG show markers of activation, only few also express Granzyme B. It was therefore proposed that most T cells are unspecific bystander T cells, attracted by the inflammatory milieu and entering the TG only due to their activation status. Entry of T cells into the TG due to activation has also been described in mice (van Lint et al. 2005), but an accumulation of HSV-1-specific T cells over time was also demonstrated (Khanna et al. 2003).

The infiltrating T cells possess clonally expanded T cell receptor (TCR) β-chains (Derfuss et al. 2007) and TCRγ-

loci (Verjans et al. 2007) indicating proliferation of these T cells to their respective antigens. Furthermore, using T cell lines from cultured TG obtained very shortly after death, Verjans et al. (2007) were able to demonstrate that the TG resident T cells were reactive against HSV-1 proteins.

Tissue-infiltrating T cells in human TG are mainly found in clusters surrounding neurons (Derfuss et al. 2007). Surprisingly, most neurons surrounded by T cells are not positive for LAT and HSV-1 DNA (Held et al. 2011). These neurons, devoid of HSV-1 but surrounded by T cells, might present foci of former reactivation from which the virus has been cleared. Several studies showed that tissue-resident memory $CD8^+$ T cells remain in skin and mucosa long after clearance of HSV-2 (Gebhardt et al. 2009; Zhu et al. 2007). In mice, most LAT^+ neurons were also found to be free of associated inflammatory cells (Feldman et al. 2002). T cells were only clustered around spontaneously reactivated neurons.

Cytokine and chemokine expression in TG

In addition to the cellular immune infiltrates, an abundant expression of cytokines and chemokines was observed in human and mouse TG latently infected with HSV-1. A significant induction of the anti-viral effectors IFN-γ, TNF-α, and CXCL10 (IP-10) as well as CCL5 (RANTES)—a chemokine involved in recruitment of T cells—could be observed in latently HSV-1-infected human TG (Theil et al. 2003a). Halford et al. (1996) described a persistent expression of the T cell-associated cytokine and chemokine mRNAs IL-2, IL-10, IFN-γ, and RANTES in latently infected mouse TG, indicating that the local lymphocytes encounter viral antigen during HSV-1 latency with sufficient frequency to remain activated. It was assessed in the mouse model that neither viral replication nor reactivation, or LAT expression in ganglia is required for this persistent elevated cytokine expression (Chen et al. 2000).

Expression of MHC class I in TG

Persistent retention of activated $CD8^+$ T cells in sensory ganglia raises the question if infected neurons do express major histocompatibility complex (MHC) class I. It was shown that MHC class I expression by neurons is inducible by IFN (Neumann et al. 1995). Moreover, an induction of MHC class I expression on Schwann and satellite cells has been described for HSV-1 lytic infection in mouse TG (Pereira et al. 1994). In humans, a strong inflammatory milieu such as in multiple sclerosis lesions was also shown to upregulate MHC class I on neurons (Hoftberger et al. 2004). It also has been proposed that the neuron supporting satellite cells function as antigen-presenting cells (van Velzen et al. 2009).

Functions of tissue-infiltrating T cells

In animal models, functional studies on tissue-infiltrating T cells are obviously more feasible than in humans. Therefore, most knowledge on how these T cells act on HSV-1 latency is derived from the mouse. It has been shown that the local $CD8^+$ T cells can keep HSV-1 from reactivating in mouse TG ex vivo cultures in a dose-dependent, antigen-specific, and MHC-restricted fashion (Liu et al. 2000; Khanna et al. 2003). This effect was shown to be mediated by IFN-γ (Liu et al. 2001) and Granzyme B (Knickelbein et al. 2008). In the mouse model with a C57Bl6 background, about 50% of TG infiltrating $CD8^+$ T cells recognizes the immuno-dominant epitope gB498-505 (Khanna et al. 2003). Still, the vast majority of $CD8^+$ T cells in latently infected mouse TG are specific for HSV-1. The subdominant epitopes mostly belong to early or late gene products expressed before viral DNA synthesis (Sheridan et al. 2009; St Leger et al. 2011). The target antigen of $CD8^+$ T cells in latently HSV-1-infected human TG still has to be resolved. The major target for human blood-derived $CD8^+$ T cells is described to be the early gene product ICP27 whereas the late proteins gD and gB are key targets for blood-derived $CD4^+$ T cells in most patients (Mikloska and Cunningham 1998). A disparity between TG-infiltrating and blood-derived T cells could be expected as it has been shown that in mice there is no replenishment of TG resident T cells from the periphery (Himmelein et al. 2011).

Even though infiltrating $CD8^+$ T cells in the TG express their full cytotoxic armor, destruction of neurons is only seen rarely in mice (Decman et al. 2005; Esaki et al. 2010) and humans (Theil et al. 2003a). In fact, mice deficient in $CD8^+$ T cells are not only unable to control HSV-1 infections but also exhibit more apoptotic neurons (Simmons and Tscharke 1992). Therefore, the major function of local $CD8^+$ T cells appears to be secretion of anti-viral cytokines like IFN-γ or TNF-α. It has been demonstrated that IFN-γ is involved in suppression of viral replication immediately after reactivation (Cantin et al. 1999), exerts a function which inhibits ICP0 expression, and further blocks reactivation at a late stage (Decman et al. 2005). A cross-regulation between ICP0, a potent transactivator of gene expression with several functions in promoting viral lytic gene expression, and IFN-γ has been proposed. ICP0 was demonstrated to be necessary to stop IFN-dependent innate host response from repressing HSV-1 (Halford et al. 2006). Moreover, $CD8^+$ T cells present in latently infected TG actually do release their cytolytic granules. It has been shown that Granzyme B, which normally initiates apoptosis

by cleavage of caspase 3, is also able to degrade ICP4, a viral IE protein required for efficient viral gene expression (Knickelbein et al. 2008).

Evidently, there need to be mechanisms to prevent CD8-mediated cytotoxic injury of infected neurons. One possibility might be the expression of the inhibitory receptors CD94/NKG2a on T cells that could interact with Qa1 on neurons as it has been shown in the mouse model (Suvas et al. 2006; Wojtasiak et al. 2004). Also, in humans, TG expression of CD94/NKG2a on infiltrating T cells was noted (van Velzen et al. 2009).

Co-infection of human TG with other viruses

One major difference between animal models and human HSV-1 infection is that animals are exclusively infected by HSV-1, whereas human TG can be infected by different viruses like the herpesviruses HSV-2, VZV, and HHV-6 (Pevenstein et al. 1999; Liedtke et al. 1993; Theil et al. 2004; Hüfner et al. 2007). It has been shown that HSV-1 and VZV can even co-occur in one neuron (Theil et al. 2003b). So, which virus is actually causing the immune infiltration?

It has been shown that the infiltrating T cells only occur in latently HSV-1-infected TG and do not co-occur with VZV (Theil et al. 2003a). Additionally, in a study using nested polymerase chain reaction (PCR) for HSV-1, VZV, and HHV-6 (Hüfner et al. 2007) only in ganglia testing positive for HSV-1, significant increases in T cell counts were found. T cell clusters were absent in dorsal root ganglia of human cadavers negative for LAT by nested PCR (Hüfner et al. 2006). T cells in human TG have been reported to be localized mainly in the maxillary and mandibular division of the TG where they co-localize with LAT^+ neurons (Hüfner et al. 2009). Analogously, in the mouse model after ocular infection, most T cells are located in the ophthalmic division of the TG (Khanna et al. 2003). This indicates HSV-1 as trigger for the immune infiltration. Furthermore, Arbusow et al. (2010) demonstrated a correlation between the expression levels of CD8 and LAT. Probably, the most convincing argument is that T cell lines derived from human TG latently infected with HSV-1 and VZV only exhibited reactivity towards HSV-1 and not VZV proteins (Verjans et al. 2007).

Taken together, there is strong evidence that the tissue-infiltrating T cells in the human TG are actually recruited by HSV-1 and not by another virus.

Control of latency by the virus

During HSV-1 latency in sensory neurons, the only abundantly expressed viral gene products are the LATs. This holds true for the mouse model of infection (Stevens et al. 1987) as well as humans (Croen et al. 1987). The 2-kb LAT stable intron, which accumulates to high levels in the neuronal nuclei, is spliced from a primary 8.3–8.5 kb polyadenylated transcript. Many functions in the establishment and maintenance of latency as well as in reactivation have been attributed to LAT as the only readily detectable transcript in latently infected neurons. This has been a field of extensive research and raised much controversy. Studies investigating the role of LAT or other viral genes in establishment or control of latency have been carried out in small animal models of infection or cell culture as this is not feasible with human samples. Most studies suggest that LAT plays a role in latency but is not essential, as most LAT^- mutants still establish latency and can also reactivate (Perng et al. 1994; Chen et al. 1997). However, LAT^- mutants show decreased numbers of latently infected neurons in TG of mice (Thompson and Sawtell 1997; Devi-Rao et al. 1994), and LAT also represses viral lytic transcripts during latency (Chen et al. 1997). A more crucial role for LAT in promoting spontaneous reactivation in rabbits (Perng et al. 1994; Hill et al. 1990) than in mice (Margolis et al. 2007a) has been shown. This may be due to the fact that spontaneous reactivation is a much more common event in rabbits than in mice. In explant cultures of mouse TG, however, LAT^- mutants show a significantly decreased reactivation rate (Carr et al. 1998). The ability of LAT to promote spontaneous reactivation has been mapped to the first 1.5 kb of the primary transcript (Perng et al. 1996). It is possible that the effect of LAT on the latency–reactivation cycle may be underestimated in animal models with a shorter lifespan and therefore a shorter latency period than in humans. In mice, it has been established that some sensory neurons containing HSV-1 DNA do not express LAT to detectable levels (Mehta et al. 1995; Chen et al. 2002b). In a recent study using LAT in situ hybridization combined with laser microdissection and quantitative PCR on human TG sections, no HSV-1 DNA containing neurons without LAT expression could be detected (Held et al. 2011). In this study, most LAT^+ neurons were also not surrounded by $CD8^+$ T cells. This proposes a more effective control of viral latency by viral or cellular factors in humans than in animal models.

One possible effect of LAT in maintaining or establishing latency could be that LAT expression is associated with increased accumulation of unspliced ICP0 transcripts (Chen et al. 2002a; Maillet et al. 2006). ICP0 is required for complete reactivation from latency with infectious virus production (Halford and Schaffer 2001; Thompson and Sawtell 2006). A counteractive role on viral IE-gene products has also been proposed for some of the recently described 16 viral microRNAs (miRNA), short RNA molecules of about 22 nucleotides in length. Most of these

miRNAs are encoded by the primary LAT transcript or by genomic regions in close proximity to LAT (Cui et al. 2006; Umbach et al. 2008, 2009; Jurak et al. 2010). These miRNAs are differentially expressed in productive versus latent infection in mice and humans (Umbach et al. 2008, 2009; Jurak et al. 2010; Held et al. 2011). The miR-H2-3p and miR-H6 were shown to reduce ICP0 and ICP4 expression in vitro (Umbach et al. 2008), respectively. However, HSV-1 mutants with reduced expression of the LAT-derived miRNAs as well as miR-H6 were able to establish and maintain latent infections in mice (Kramer et al. 2011). It is not yet clear whether viral miRNAs as well as LAT might play a more crucial role in humans. Two more small RNAs have been mapped to the LAT region: sRNA1 and sRNA2, both exhibiting functions in inhibiting productive infection and apoptosis in mice (Perng and Jones 2010).

Latent HSV-1 DNA is in a heterochromatic state with histone marks typical for a repressed chromatin structure (Knipe and Cliffe 2008). The enhanced assembly of heterochromatin in promoters of lytic genes correlates with the presence of LAT (Wang et al. 2005b). It was therefore proposed that LAT silences viral lytic genes by inducing heterochromatin formation in essential regions of the viral genome.

In mice, LAT further plays a role in cell tropism of HSV-1. A small part of the LAT 5′ exon defines which neuronal cell type becomes latently infected (Imai et al. 2009). HSV-1 LAT was mostly detected in $A5^+$ neurons whereas HSV-2 LAT mostly occurred in $KH10^+$ neurons (Margolis et al. 2007b). This is due to the fact that $A5^+$ neurons are non-permissive for productive infection by HSV-1 (Bertke et al. 2011).

Moreover, LAT inhibits apoptosis and thereby promotes survival of infected neurons (Perng et al. 2000; Hamza et al. 2007). Correct splicing of the 2 kb LAT is necessary for this function (Kang et al. 2003). LAT inhibits caspase 8- and caspase 9-induced apoptosis (Henderson et al. 2002) as well as caspase 3 activation by Granzyme B released from $CD8^+$ T cells (Jiang et al. 2011). Another function of LAT in promoting neuronal survival is the induction of T cell exhaustion in latently infected mouse TG (Allen et al. 2011).

Regarding the properties of LAT, one might speculate that LAT restricts spontaneous reactivation by reducing expression of specific genes like ICP0 or ICP4, thereby ensuring that a short interruption in the repression of viral genes does not lead to reactivation. The anti-apoptotic function of LAT might be very important during all steps of latency when expression of other viral anti-apoptotic genes is limited or absent. Without inhibition of apoptosis, latently infected neurons could die in response to viral infection and thereby reduce the number of latent HSV-1 genomes.

Control of latency by cellular factors

Cellular factors also have been implied in the control and establishment of HSV-1 latency. Differential distribution of proteins in neuronal and non-neuronal cells like HCF1, as well as differential regulation of IE and LAT promoters by neuronal specific factors have been described (reviewed in (Perng and Jones 2010)). Furthermore, sensory neurons in contrast to other cells are fully differentiated cells which do not divide anymore and therefore provide a completely different environment to HSV-1. Very recently, it has been shown in mice that neurons positive for the marker A5 are not permissive for productive but latent HSV-1 infection (Bertke et al. 2011), directly showing differential regulation of the viral life cycle in a subset of neurons. Whether only specific neuronal cell types in human TG become infected also remains to be elucidated.

Triggers for reactivation

An important difference in HSV-1 latency in mice and humans is the frequency of spontaneous reactivation. This may be due to the fact that the HSV-1 protein ICP47 has a lower affinity for mouse TAP1/2 than for human TAP1/2 (Orr et al. 2007). Therefore, HSV-1 can less efficiently block MHC class I presentation of antigens in mice, which leads to a more efficient immune control of the virus. Actually, in mice, most TG resident $CD8^+$ T cells are specific for HSV-1 (St Leger et al. 2011). These $CD8^+$ T cells are able to block viral transcription even at late stages (Decman et al. 2005). In humans, it seems that a higher percentage of the local $CD8^+$ T cells are unspecific bystander cells (Verjans et al. 2007), and therefore HSV-1 might be able to escape from the host immune system more easily after initiating viral transcription.

The most common trigger for reactivation of latent HSV-1 is stress, which has been shown to induce reactivation in mice by reducing the number and functionality of HSV-1-specific $CD8^+$ T cells (Freeman et al. 2007; Bonneau 1996). Also, in humans, immunosuppression caused by stress led to increased reactivation of HSV-2 (Pereira et al. 2003). Glucocorticoids reduce T cell numbers in TG of mice latently infected with HSV-1 (Himmelein et al. 2011), regulate gene expression, and induce changes in the chromatin status (Adcock 2000), thereby possibly activating viral gene expression. It has also been demonstrated that the neuronal excitation status influences efficiency of HSV-1 viral replication in cultured neurons (Zhang et al. 2005): Increased neuronal excitability inhibited viral replication, whereas decreasing the activity of neurons enhanced viral replication. Taken together, reactivation of HSV-1 seems to be triggered by signals which lead to an increase

in transcription activity of the host neuron (Wagner and Bloom 1997). The molecular mechanism might be explained by translocation of HCF1 into the nucleus of stressed neurons. If then, the increased transcription activity allows VP16 de novo synthesis, activation of α-promoters could occur. LAT and $CD8^+$ T cells act on repressing further viral gene expression, but if these control mechanisms are overrun, limited viral replication takes place. Resulting viral particles are subsequently transported by anterograde axonal transport to the neuronal termini. Presumably, as no sensational loss is associated with repeated reactivation, no or only limited neuronal death occurs during release of virus. Apparent lesions are less frequent than short subclinical HSV reactivations with asymptomatic shedding of the virus as demonstrated by a study on humans (Mark et al. 2008).

Reactivation from human TG is hard to study, as so far no reactivation event with synthesis of viral proteins could be observed (Theil et al. 2003a; Derfuss et al. 2007).

Conclusion

We have summarized here the current understanding of the control mechanisms of HSV-1 latency in humans and small animal models.

Viral latency is maintained by a number of different mechanisms including specific neuronal factors and viral factors like LAT, viral miRNAs, or the epigenetic regulation of the viral genome. When HSV-1 escapes these control mechanisms, the local CD8+ T cell response can step in to prevent full reactivation.

Most knowledge about the function of viral transcripts and host factors in maintaining latency was gained from small animal models of HSV-1 infection. It remains to be elucidated whether the mechanisms learned from animal models are applicable to HSV-1′s natural host.

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