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Review

Reactivation from latency by α-herpesvirinae subfamily members: a stressful situation

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ABSTRACT

Acute infection of a permissive host by a α-herpesvirinae subfamily member leads to expression of all viral genes and high levels of virus shedding. Following acute infection, most α-herpesvirinae subfamily members establish and maintain life-long latency in sensory neurons. In contrast to productive infection during acute infection or infection of permissive cultured cells, viral gene expression is limited to the latency-associated transcript locus. The ability of these viruses to periodically reactivate from latency is crucial for virus transmission and recurrent disease is due to reactivation from latency. For example, herpes simplex virus type 1 (HSV-1) and HSV-2 are important human pathogens that cause recurrent eye disease, including blindness, and recurrent genital infections, respectively. External stressors disrupt the maintenance of latency and increase the incidence of reactivation from latency. Regardless of their mechanism of action, external stressors that promote reactivation from latency must initiate expression of key regulatory viral genes in latently infected neurons. Most external stressors that induce reactivation also suppress immune responses. The viral and cellular factors that regulate reactivation from latency and recurrent disease are discussed in this review.

KEYWORDS: α-herpesvirinae subfamily, HSV-1, BHV-1, reactivation from latency, stress

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INTRODUCTION

Members of the α-herpesvirinae subfamily are important viral pathogens of their respective hosts. Following acute infection, these viruses typically establish a latent infection in sensory neurons that innervate the site of acute infection, reviewed in [1-4]. In contrast to acute infection, viral gene expression is severely restricted during latency and infectious virus is not readily detectable. A latent infection is periodically interrupted by an external stimulus, which leads to reactivation from latency and shedding of infectious virus at peripheral sites. Stressful stimuli correlate with increasing the incidence of reactivation from latency, which is crucial for virus transmission and can lead to recurrent disease in certain circumstances.

Most recurrent clinical outbreaks due to herpes simplex virus type 1 (HSV-1) or HSV-2, including herpetic stromal keratitis (HSK), cold sores, recurrent genital outbreaks, and even certain cases of life-threatening herpetic-induced encephalitis are the direct result of reactivation from latency, reviewed in [1-7]. Acute ocular HSV-1 infections only induce clinically apparent disease in 1-6% of patients [8, 9]. In spite of the availability of anti-HSV drugs, HSK is still the most common infectious cause of corneal opacity that can eventually lead to blindness in the developed world. HSK is characterized by tissue destruction, edema, opacification, corneal scarring, and neovascularization [10]. Understanding the mechanism by which α-herpesvirinae subfamily members

reactivate from latency may lead to new therapeutic strategies that target reactivation from latency and recurrent disease.

1. Acute infection leads to life-long latency in sensory neurons

Acute infection of the natural host with a α-herpesvirinae subfamily member generally leads to programmed cell death, inflammation and high levels of virus production, reviewed in [1-5]. If infection is initiated within the oral, nasal, or ocular cavity, the primary site for latency is sensory neurons in trigeminal ganglia (TG). A genital infection typically leads to establishment of latency in sensory neurons within dorsal root ganglia. Viral gene expression and infectious virus are generally detected in TG from 2-6 days after infection. Lytic cycle viral gene expression is subsequently extinguished, a significant number of infected neurons survive and these neurons harbor viral genomes. The ability of herpes simplex virus type 1 (HSV-1), HSV-2, bovine herpesvirus 1 (BHV-1), and other α-herpesvirinae subfamily members to periodically reactivate from latency is crucial for virus transmission. Furthermore, reactivation from latency can lead to recurrent disease in individuals latently infected with HSV-1 or HSV-2.

Viral gene expression in cultured cells occurs in three well-defined phases: immediate early (IE), early (E), or late (L). All α-herpesvirinae subfamily members encode two key transcriptional regulators; infected cell protein 0 (ICP0) and ICP4. ICP0 is a promiscuous trans-activator of viral gene expression, interferes with innate immune responses, and disrupts the anti-viral promyelocytic leukemia (PML) containing nuclear bodies, reviewed in [11-13]. All ICP0 orthologues contain a well-defined C_3HC_2 Zinc RING finger that is crucial for their E3 ubiquitin ligase activity. ICP0 proteins also interfere with innate immune responses, which allow viral growth *in vivo*. ICP4 orthologues specifically bind DNA, and there are approximately 100 ICP4 binding sites in the HSV-1 genome. ICP4 stimulates E and L gene expression by binding to viral promoters and recruiting RNA polII cofactors. A tegument protein, VP16, stimulates IE transcription by interacting with two cellular proteins (Oct1 and host cellular factor 1), and this protein complex binds to specific sequences in IE promoters; thus VP16 specifically trans-activates all IE promoters [14-16]. E proteins, in general, are non-structural and promote viral DNA replication. L proteins comprise the infectious virus. Although a vigorous immune response occurs at the initial site of infection, viral particles enter the peripheral nervous system via cell-cell spread. The cascade of viral gene expression has been primarily studied in cultured cells; however, it is assumed that the same well-ordered cascade occurs in mucosal layers during acute infection.

2. The latency-reactivation cycle is comprised of at least three steps

Despite a vigorous immune response during acute infection, HSV-1 establishes latency in ganglionic sensory neurons, typically TG or sacral dorsal root ganglia [1, 17]. Although TG is a primary site of latency following ocular, oral, or intranasal infection [18-20], latent HSV-1 can also be detected in human adult nodose ganglia and the vagus nerve [21, 22]. Up to 40% of sensory neurons can be latently infected [23-27]. HSV-1 genomic DNA has also been detected in the central nervous system of a significant number of humans [18, 28, 29].

The steps defining the latency-reactivation cycle have been operationally divided into establishment, maintenance, and reactivation from latency (Figure 1). Establishment of latency includes entry of the viral genome into a sensory neuron followed by a brief period where lytic cycle viral gene expression and infectious virus can be detected in TG. Viral gene expression is then extinguished. Maintenance of latency is operationally defined as a period when infectious virus is not detected by standard virus isolation procedures and lasts for the life of the host. In general, abundant expression of lytic cycle viral genes that are required for productive infection does not occur and most importantly latently infected neurons survive.

An external stressor can initiate reactivation from latency; consequently abundant lytic cycle viral gene expression is induced. Stress has been defined as a stimulus that activates the hypothalamic-pituitary-adrenal axis and/or the sympathetic

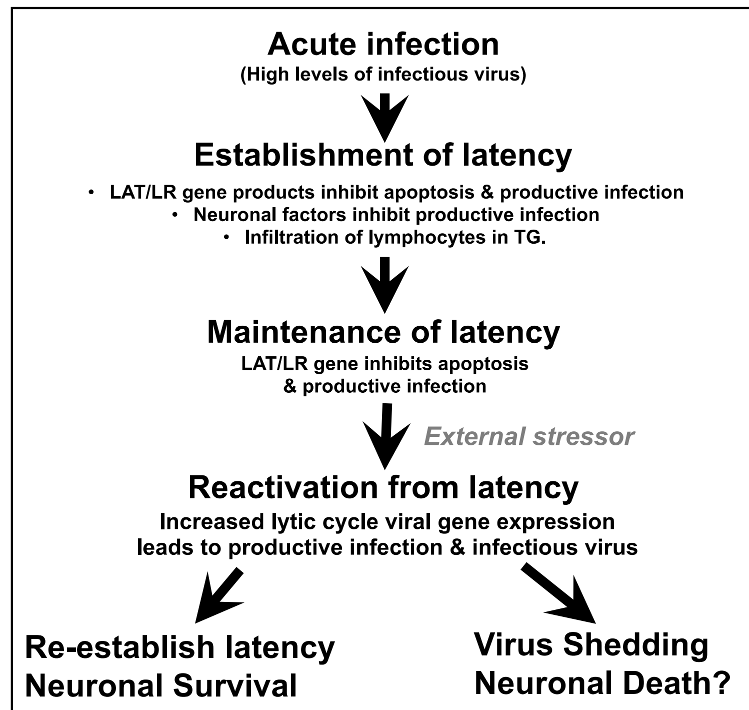

Figure 1. Schematic of steps that comprise the latency-reactivation cycle.

nervous system to allow a multi-cellular organism to respond to a threat [30]. Stress also frequently decreases immune functions, reviewed in [31]. During reactivation from latency, abundant viral gene expression is detected in sensory neurons and infectious virus can be isolated from TG, ocular swabs, and/or nasal swabs. Although the exact percentage of sensory neurons that support successful reactivation is not known, we hypothesize that most latently infected neurons re-establish latency following a stressful stimulus and these neurons survive. In fact, most neurons latently infected with BHV-1 re-establish latency following treatment with the synthetic corticosteroid dexamethasone (DEX) [32].

3. Viral gene expression during latency is restricted and promotes latency

3.1. Viral gene products expressed during latency promote survival of infected neurons

With the exception of human varicella zoster virus, nearly all other α-herpesvirinae subfamily members encode a latency-associated transcript (LAT) that is abundantly expressed during establishment and maintenance of latency, reviewed in [1-5]. The BHV-1 LAT orthologue is referred to as the latency related (LR) RNA. LAT coding sequences and the LR gene are antisense with respect to the ICP0 gene (Figures 2 and 3A). LAT and the LR gene are complex loci that encode more than one factor. It is likely that each of these factors regulate specific aspects of the life-long latency-reactivation cycle. A comparison of the products encoded by the HSV-1 LAT locus and LR gene is presented below.

With respect to HSV-1 [33-39], HSV-2, or BHV-1, LAT expression is important for reactivation from latency, reviewed in [2, 4]. In fact, a mutant containing a triple stop codon insertion near the 5' terminus of the first ORF (ORF2) in the LR gene (LAT homologue) prevents DEX-induced reactivation from latency in calves [40].

Both HSV-1 LAT and the LR gene interfere with apoptosis in cultured cells as well as *in vivo* [41-46]. The anti-apoptosis functions of HSV-1 LAT correlate with promoting spontaneous reactivation in rabbits [42, 47], in part by promoting the maintenance of latency [45]. Inhibiting apoptosis

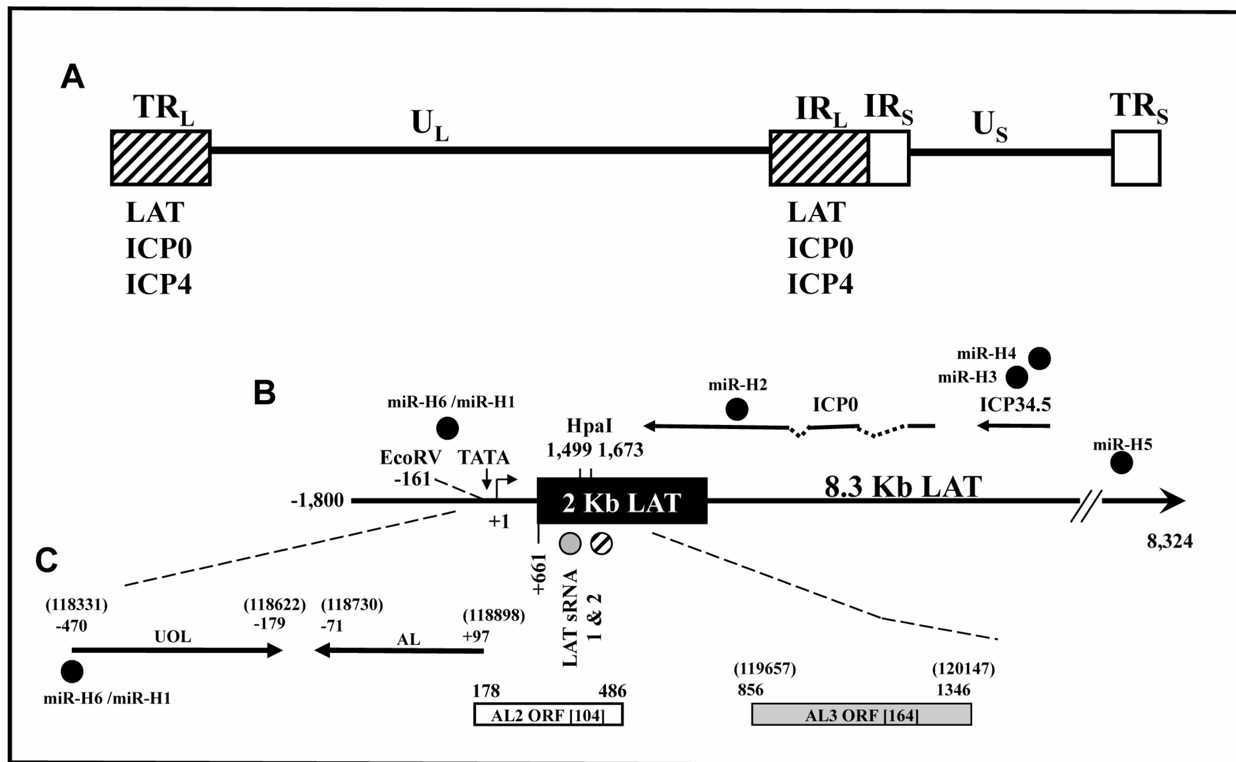

Figure 2. Schematic of products encoded within the HSV-1 LAT locus.

Panel A: Location of the unique long (U_L) and unique short (U_S) regions of the HSV-1 genome. The repeats, terminal repeat long (TR_L), internal repeat long (IR_L), internal repeat short (IR_S), terminal repeat short (TR_S), are denoted by the rectangles. The bICP0 gene is present within both repeats and is denoted by the grey rectangle.

Panel B: Schematic of genes within the long repeats that contain the LAT locus. The large arrow indicates the primary LAT transcript. The solid rectangle represents the very stable 2 kb LAT intron. The start of LAT transcription is indicated by the arrow at +1 (genomic nucleotide 118801). Several restriction enzyme sites and the relative locations of the ICP0 and ICP34.5 transcripts are shown for reference. The location of the 6 micro-RNAs (miR-H1-6) that are located within the 8.3 kb LAT are shown. The grey and stippled circles denote the position of two LAT small RNAs that are encoded within the first 1.5 kb LAT coding sequences.

Panel C: Positions of UOL transcript, AL transcript, and ORFs located on the opposite strand of LAT (AL2 and AL3) are shown. The number of amino acids of AL2 and AL3 are in brackets. Nucleotide positions relative to the start of LAT transcription are not shown in parenthesis. Numbers in parentheses represent HSV-1 nucleotide positions.

appears to be the most important function of LAT because three different anti-apoptosis genes [48-51] restore wt levels of spontaneous reactivation to a LAT null mutant. Two LAT small non-coding RNAs that are not micro-RNAs (sRNA1 and sRNA2; Figure 2B) cooperate to inhibit cold-shock-induced apoptosis in transiently transfected mouse neuroblastoma cells [52]. In contrast to HSV-1 LAT, ORF2 as well as two micro-RNAs encoded within the BHV-1 LR gene interfere with apoptosis in transiently transfected cells suggesting they promote neuronal survival following infection [53, 54]; in particular during establishment and maintenance of latency (Figure 1). A number of studies have provided evidence that the BHV-1 LR gene and HSV-1 LAT encode three common functions that promote survival of latently infected neurons: 1) inhibit apoptosis as described above, 2) inhibit lytic cycle viral gene expression [52, 55-57], and 3) promote a mature neuronal phenotype [58-61]. Since HSV-1 LAT as well as LAT encoded micro-RNAs [62] and expression of

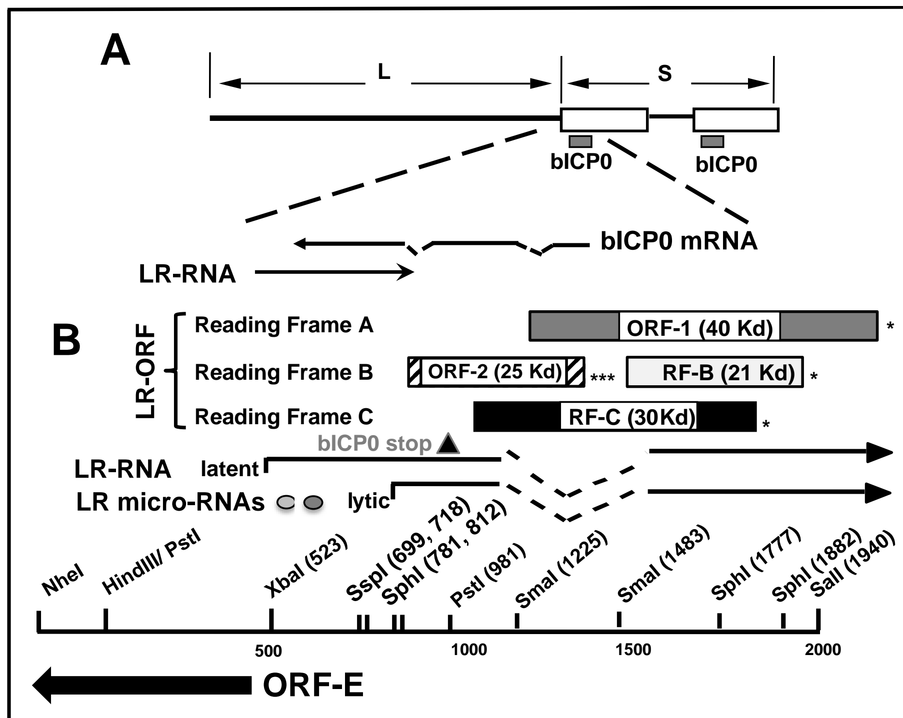

Figure 3. Schematic of products encoded within the BHV-1 LR gene.

Panel A: Location of the unique long (UL) and unique short (US) regions of the BHV-1 genome. The repeats are denoted by the open rectangles. The bICP0 gene is present within both repeats and is denoted by the grey rectangle. The dashed lines within the bICP0 mRNA are intron sequences.

Panel B: Partial restriction map, location of the two LR-specific micro-RNAs, and LR ORFs. The 3' terminus of bICP0 is denoted by the black triangle. ORF-1 and ORF-2 are located in the LR gene and have the potential to encode a 40 or 25 kd protein, respectively. Reading Frames B (RF-C) and C (RF-C) contain an open reading frame, but lacks an initiating Met. The (*) denote the position of stop codons that are in frame with the respective ORF. The location of ORF-E, which is antisense with respect to the LR ORFs and does not overlap the bICP0 ORF is denoted.

all BHV-1 LR gene products [32, 56, 58] decrease during the early stages of reactivation from latency, it appears that LAT and the LR gene do not directly stimulate reactivation from latency. However, these genes are predicted to establish and maintain latency in a pool of neurons that have the potential to reactivate from latency following an external stressful stimulus.

3.2. The HSV-1 LAT locus encodes multiple factors

A study by Umbach *et al.* [57] concluded LAT is a micro-RNA (miRNA) precursor that encodes four miRNAs plus two within LAT promoter sequences (Figure 2 B and C). LAT miR-H6 inhibits ICP4 protein levels but not ICP4 RNA levels. ICP0 protein levels, but not RNA levels, are inhibited by another LAT miRNA, miR-H2. Levels of the late viral protein ICP34.5, which is a neurovirulence factor, are reduced by miR-H3 and miR-H4 in transient transfection studies [63, 64]. The miRNAs that are abundantly expressed during latency are not essential for latency using a mouse model of infection [65]. Since the six LAT-specific miRNAs are not located within the first 1.5 kb of LAT coding sequences, which is crucial for reactivation from latency in small animal models of infection [33, 35], this result is perhaps not that surprising. Collectively, these studies indicate that the miRNAs encoded from the LAT locus have the ability to inhibit viral gene expression, which would favor establishment and life-long maintenance of latency in humans.

Two additional small RNAs (s-RNAs) are encoded within the first 1.5 kb of LAT coding sequences (LAT s-RNA1 and s-RNA2) [66] (Figure 2B).

Expression of LAT s-RNA1 and s-RNA2 is readily detected in TG of latently infected mice [52]. LAT s-RNA2 inhibits ICP4 protein expression, but not RNA expression. LAT s-RNA1 inhibits productive infection more than 100-fold in transient transfections assays when cotransfected with the genome from a LAT null mutant, whereas LAT s-RNA2 only inhibits productive infection 5-fold [52]. These LAT s-RNAs are not miRNAs because they lack Dicer cleavage sites and a mature miRNA band that migrates between 21-23 nucleotides was not detected. LAT s-RNA1 and s-RNA2 may not have been identified using the methods described by Umbach *et al*. [57] because they size-selected RNA species migrating between 17 and 30 nucleotides, and LAT s-RNA1 is 62 nt long and LAT s-RNA2 is 36 nt long. Interestingly, a recent study suggests a mechanism whereby LAT upregulates expression of the herpesvirus entry mediator (HVEM) through binding of the two LAT s-RNAs to the HVEM promoter and that increased HVEM expression interferes with immune responses in the latent microenvironment and consequently increases the survival of latently infected neurons [67]. LAT can also inhibit functional maturation of dendritic cells [68] and granzyme B-mediated programmed cell death [69]. These findings suggest that LAT can function as an immune evasion gene, which maintains latency by interfering with immune-mediated recognition of infected neurons [68].

Sequences that encompass the LAT locus also encode additional transcripts (Figure 2B). For example, novel transcripts within the LAT promoter region have been described [70]. Furthermore, a transcript and protein, UOL (Upstream of LAT), is encoded within the LAT promoter regulatory region [71]. Deletion of UOL does not dramatically reduce the spontaneous reactivation phenotype in rabbits [72]. The antisense to LAT (AL) transcript is expressed within the first 1.5 kb of LAT coding sequences and the start site of the LAT promoter; the AL transcript also appears to encode a protein [73] (see Figure 2B for location of UOL and AL). An AL3 transcript encoded within the first 1.5 kb of LAT coding sequences is expressed during productive infection and in TG of latently infected mice [74]. An AL3 protein is expressed in mouse neuroblastoma cells transfected with an AL3 expression vector and TG of latently infected mice; however the function of this protein is not known. The AL3 protein is not detected during productive infection, in part, because the 5' terminus of the AL3 transcript is downstream of the first in frame methionine of AL3. It is not currently known whether a transcript encompassing AL2 is expressed during productive infection or during latency. No published study has tested whether AL2 or AL3 is important for the HSV-1 latency-reactivation cycle in small animal models.

Primary sensory neurons are a diverse population of cells with respect to cell surface markers, cellular morphology, gene expression, and responses to certain stimuli. A panel of monoclonal antibodies that recognize specific cell surface markers can distinguish neuronal subtypes and these antibodies have been used to correlate interactions between HSV and specific neuronal populations [75]. These studies provide compelling evidence that sequences in HSV-1 LAT confer a preference for establishing latency in A5+ sensory neurons within TG, whereas HSV-2 LAT promotes establishment of latency in KH10+ sensory neurons in TG [75, 76]. Conversely, productive infections with HSV-1 and HSV-2 are regulated differently in A5+ and KH10+ sensory neurons. Additional studies clearly demonstrated that cis-acting sequences in the respective LATs were responsible for specifying neuronal tropism [77]. The LAT enhancer has also been proposed to contain cis-acting sequences, including CTCF insulators that regulate expression of key immediate early genes (ICP0, ICP4, and ICP27 for example) in a cell-type specific manner [78]. Neuronal-specific transcription factors are believed to work via the LAT enhancer to stimulate LAT expression; conversely, IE promoters are repressed. In non-neuronal cells, IE promoters would be more active and would not be inhibited by the LAT enhancer. In summary, these studies demonstrated LAT is a complex locus that plays a role in maintaining life-long latency in human sensory neurons. The importance of LAT may have been underestimated using mouse and rabbit models that measure latency in terms of weeks and months whereas latency in humans must be maintained for decades.

3.3. The BHV-1 LR gene encodes functional proteins and micro-RNAs in latently infected neurons

As with HSV-1 LAT, LR-RNA sequences are antisense and overlap the BHV-1 ICP0 orthologue, bICP0 (Figure 3A). In contrast to LAT, the LR gene is a single copy gene (Figure 3A). The LR gene contains two well-defined open reading frames (ORF2 and ORF1; Figure 3B) and two reading frames that lack an initiating methionine (RF-B and RF-C). As a result of alternative splicing of polyA+ LR-RNA in TG of infected calves [79, 80], ORF2 can be fused with ORF1 protein coding sequences or RF-B. Splicing of LR-RNA in TG at one day after infection or during latency yields an intact ORF2. ORF2 protein expression, not merely LR-RNA expression, is required for inhibiting apoptosis in transiently transfected cells [81, 82] suggesting ORF2 promotes survival of infected neurons during establishment and maintenance of latency (Figure 1). An alternatively spliced LR-transcript encodes a protein that contains most of ORF2 fused with ORF1 [79, 80] that stably interact with the cellular transcription factor C/EBP-alpha [83]. C/EBP-alpha RNA and protein levels increase in TG neurons during DEX-induced reactivation from latency. Since over-expression of C/EBP-alpha enhances productive infection, binding of C/EBP-alpha by the novel ORF2 isoform may reduce the efficiency of productive infection.

ORF2 interacts with Notch1 and Notch3, components of the Notch signaling pathway [84]. Notch receptor family members (Notch1-4) are membrane tethered transcription factors that regulate embryogenesis, development, and differentiation of nearly all cell types [85, 86]. Furthermore, Notch promotes neuronal maintenance, development, and differentiation [87-89]. Notch3 [90] and Notch1 [91, 92] promote cell survival by activating a protein kinase, AKT, which inhibits apoptosis. Other studies demonstrated that Notch family members induce apoptosis [85, 86] suggesting Notch influences cell survival in a cell-type dependent fashion. When the Notch receptor is engaged by one of its five transmembrane ligands (Jagged1, Jagged2, Delta-like1, Delta-like3, or Delta-like4), the Notch intracellular domain (ICD) is cleaved by specific proteases, and subsequently translocates to the nucleus. In the nucleus, Notch ICD interacts with members of the CSL family of transcriptional factors, CBF1, Su(H), or Lag1 (also referred to as RBPJ binding proteins); thus, activating genes occupied by a CSL family member.

ORF2 overcomes the ability of Notch to inhibit neurite formation in transiently transfected mouse neuroblastoma cells [58]. In the context of the latency-reactivation cycle, this is important because activated Notch signaling in neurons inhibits neurite sprouting [88, 93-96] and axon repair [97], which can result in neuronal cell death [98, 99]. Conversely, neurite sprouting is synonymous to regeneration of damaged axons and dendrites [97]. Although many of these studies were performed with neurons derived from the CNS or in the CNS itself, activated Notch also interferes with neuronal differentiation in the ophthalmic branch of TG [100]. Notch1, but not Notch3, also enhances BHV-1 productive infection [84]. Only Notch1 stimulates the BHV-1 immediate-early transcription unit 1 (IEtu1) and bICP0 early promoters; conversely Notch1 and Notch3 trans-activate the late glycoprotein C (gC) promoter. ORF2 interferes with the ability of Notch1 to trans-activate the bICP0 early promoter and Notch1 or Notch3 mediated activation of the gC promoter [84]. Interestingly, Notch3 RNA levels [84] and the Notch signaling pathway [101] are induced during DEX-induced reactivation from latency suggesting the Notch signaling pathway influences survival of an infected neuron by more than one mechanism.

A small ORF located within the LR promoter is designated ORF-E (Figure 3B). ORF-E is antisense to the LR transcript, and downstream of bICP0 coding sequences, but does not overlap bICP0. The initiating methionine codon for ORF-E is located at nucleotide 697 and the terminating codon at nucleotide 297. The LR promoter contains multiple cis-acting motifs and a neuronal-specific binding domain [102-104]. LR promoter sequences also contain a long AT-rich motif (40/53 nucleotides are A or T) that may initiate ORF-E transcription. A transcript that encompasses ORF-E is expressed in productively infected bovine cells, and TG of latently infected calves [105]. When ORF-E protein coding

sequences are fused in frame with green fluorescent protein (GFP) sequences, GFP protein expression is detected in the nucleus of mouse or human neuroblastoma cells and promotes neurite formation in mouse neuroblastoma cells [106].

The LR gene also encodes two micro-RNAs located upstream of ORF2 that are expressed during latency (Figure 3B). Both micro-RNAs have the potential to base-pair with bICP0 mRNA sequences [107]. These micro-RNAs reduce bICP0 protein levels, but not RNA levels, in transient transfection assays, which correlate with their ability to interfere with productive infection. Furthermore, non-protein coding RNA sequences contained within micro-RNA coding sequences can reduce the growth rate of mammalian cells [108, 109]. It is well established that small non-coding RNAs regulate gene expression [110, 111], promote neuronal differentiation [112], or inhibit apoptosis [113] suggesting that the non-protein coding RNAs encoded within the LR gene and LAT locus regulate certain aspects of the latency-reactivation cycle.

4. Model systems to study α-herpesvirus reactivation from latency

With respect to HSV-1, there are several small animal model systems that have been used to study the latency-reactivation cycle. A summary of the main models and the salient features of these models are summarized below. A summary of animal α-herpesviruses that have contributed to our understanding of the latency-reactivation cycle is also included.

4.1. *In vivo* reactivation of HSV induced by external stimuli

Heat stress-induced reactivation from latency is reported to be the most efficient method for reactivating HSV-1 from latently infected mice *in vivo* [114]. For these studies, a mouse is placed in a 50-ml conical tube that contains 5-mm-diameter holes drilled throughout each tube. The mice are then incubated in a 43 ºC water bath for five to ten minutes [114, 115]. Mice are then removed, dried off with a towel, and placed back in their cages. Within 18-24 hours after heat stress, infectious virus can be detected in ocular swabs or lytic cycle viral protein expression is detected in TG neurons [114]. Synthesis of VP16 has been reported to play a crucial role during the initial stages of heat stress-induced reactivation from latency, which has been coined the exit from latency [116]. Repeated episodes of heat stress-induced reactivation from latency can occur, as judged by lytic cycle viral protein synthesis in TG or infectious virus shedding, when a virulent strain of wt HSV-1 is used to establish latency in Swiss Webster mice [117]. When latency is established with a LAT null mutant, infectious virus and lytic cycle viral gene expression in TG is nearly undetectable after repeated episodes of heat stress-induced reactivation from latency. This provides compelling evidence that LAT plays a critical role during the maintenance of latency following multiple reactivation stressors. Since LAT promotes survival of infected neurons by inhibiting apoptosis and productive infection, reviewed in [4, 5], this result supports the concept that LAT maintains a pool of latently infected neurons that can reactivate from latency.

Ultraviolet (UV) light can stimulate reactivation from latency and recurrent eye disease in latently infected mice [118, 119]. UV light will also stimulate cutaneous HSV-1 reactivation [120] and HSV-2 reactivation from latency [121]. Interleukin 6, which is induced by UV light [122] promotes UV-induced ocular reactivation from latency in mice [123]. UV light has additional effects on immune responses and inflammatory response [124] and enhances HSV-1 replication in human fibroblasts, regardless of DNA repair capabilities of these cells [125, 126]. The cellular transcription factor c-jun is activated by UV light via phosphorylation by the Jnk kinase [127]. Intron-1 of the HSV-1 ICP0 gene contains multiple-repeated binding sites for the YY1 repressor and two transcriptional activators, AP-1 and Sp-1 [128]. The HSV-2 promoter that drives expression of the large subunit of ribonucleotide reductase also contains two consensus AP-1 binding sites [129, 130]. In summary, UV light can increase the incidence of reactivation from latency by stimulating viral gene expression and replication as well as influencing immune regulators.

Iontophoresis of epinephrine into the cornea of mice, rabbits, or squirrel monkeys latently infected with HSV-1 can induce reactivation from latency

[131-133]. In rabbits, this procedure consistently stimulates virus shedding and recurrent eye disease, reviewed in [134]. Although this is a consistent procedure to induce shedding of infectious virus from the ocular cavity of latently infected animals, it is technically difficult to perform. Consequently, the molecular aspects of reactivation from latency have not been pursued using this technique.

4.2. Spontaneous reactivation in small animal models latently infected with HSV

Rabbits that are latently infected with certain HSV-1 strains can periodically undergo spontaneous reactivation from latency. Guinea pigs latently infected with HSV-2 can also undergo spontaneous reactivation from latency. For example, rabbits latently infected with the McKrae strain of HSV-1 reproducibly reactivate from latency [33, 35, 135-137]. Virus is shed from the ocular cavity and deletion of the first 1.5 kb of LAT coding sequences significantly reduces the incidence of spontaneous reactivation from latency. Furthermore, there is a correlation between the ability of LAT to inhibit apoptosis and exhibit wild-type levels of spontaneous reactivation from latency [42].

In mice, it is estimated that approximately one neuron in 10 TG is expressing lytic cycle viral proteins (ICP4 or thymidine kinase), which the authors conclude is "spontaneous molecular reactivation" [138]. Infectious virus is not detected in mice undergoing spontaneous molecular reactivation by standard virological assays. Other studies also provided evidence that lytic cycle viral RNA [139] and protein expression [140] sporadically occur in sensory neurons during latency. Low levels of infectious virus can be detected in TG of mice latently infected with HSV-1 [141]. Regardless of the interpretation, it is clear that during latency lytic cycle viral gene expression can occur in a subset of sensory neurons, and this phenomenon is referred to as "animation" of the latent viral genome [142]. These results imply that low levels of infectious virus are produced in certain circumstances following spontaneous reactivation in mice. Virus shedding in latently infected mice does not occur at high frequencies following a reactivation stimulus [143], in part, because a viral gene (ICP47) that inhibits peptide presentation via the major histocompatibility complex I pathway does not work efficiently in mice [144].

HSV-2 also spontaneously sheds virus long after acute infection is resolved in guinea pigs, and expression of LAT is important for spontaneous reactivation [145]. HSV-2 LAT coding sequences do not apparently play a role in the latency-reactivation cycle, but promoter sequences are important [146].

4.3. Explant-induced HSV reactivation from latency

Explant of TG from mice latently infected with HSV-1 has been extensively used to study reactivation from latency. Shedding of infectious virus occurs frequently and by 14 hours after explant infectious virus can be detected [147]. The efficiency of explant-induced reactivation from latency in Swiss Webster mice, but not Balb/C mice, is reduced when infected with a LAT null mutant versus wild-type HSV-1 McKrae strain [148]. During early stages of explant-induced reactivation from latency, chromatin remodeling occurs at the ICP0 promoter, a decrease in LAT expression precedes ICP0 transcription [149], and these events preferentially occur in viral strains that efficiently reactivate from latency [150]. An independent study found decreased expression of LAT and LAT-encoded micro-RNAs during reactivation from latency [62]. The cellular transcription factors HCF-1 and RNA polII are recruited to the ICP0 promoter as well as other IE promoters [151]. Remodeling of viral chromatin may be stimulated by the cellular histone acetyl transferase p300/CBP, which stimulates reactivation from latency following explant [152]. Viral transcription has been reported to be "disorganized" during explant-induced reactivation from latency [62], and induction of apoptosis by the synthetic corticosteroid DEX and 2((3-(2,3-dichlorophenoxy)propyl)amino)-ethanol was reported to accelerate reactivation [153]. Explant-induced reactivation also preferentially occurs in neurons that express cyclin dependent kinase 2 (cdk2) and cdk4 [154]. This finding is intriguing because cdk2 and cdk4 expression stimulates neuronal apoptosis [155, 156] and cdk activity may stimulate viral DNA replication by increasing dNTP levels. Interestingly, caspase 3, the well-accepted "point of no return" during

apoptosis stimulates HSV-1 reactivation from latency [157] further supporting the idea that apoptosis induction induces reactivation from latency.

DEX induces cellular transcription factors in TG neurons, which were subsequently found to stimulate ICP0 promoter activity [54]. These transcription factors are also rapidly expressed following TG explant [54]. For example, Krüppel-like transcription factor 15 (KLF15) stimulates HSV-1 ICP0 promoter activity more than 400-fold, but has little effect on other HSV-1 promoters, including VP16 and ICP4 [54]. KLF4, SPDEF (Sam-pointed domain containing Ets transcription factor), and Slug stimulate ICP0 promoter activity more than 100-fold. The finding that KLF4 and KLF15 are stimulated during DEX-induced reactivation from latency is provocative because KLF family members resemble the Sp1 transcription factor family and both transcription factor families interact with GC rich motifs in promoters; reviewed in [158, 159]. The HSV-1 genome and other α-hepesvirinae subfamily members are GC-rich and many viral promoters contain Sp1 binding sites as well as additional GC-rich motifs [158] suggesting KLF family members regulate viral transcription during reactivation from latency.

4.4. Neuronal cultures prepared from rodents

Neuronal cultures prepared from rodents that are infected with HSV-1 have been used extensively to study the latency-reactivation cycle. For example, sympathetic neurons from embryonic rats can be cultured as a pure population of cells that depend on nerve growth factor (NGF) for their survival. Following infection with HSV-1, a quiescent infection resembling latency can be established by treating cultures with the anti-viral drug acyclovir for six days [160, 161]. Withdrawal of NGF from cultures leads to reactivation from latency suggesting NGF promotes maintenance of the quiescent or latent infection. Recent studies using this model demonstrated that when NGF binds to its receptor, TrkA activates the PI-3 kinase and the serine/threonine protein kinase AKT; consequently a latent infection is maintained [62]. Although epidermal growth factor and glial derived neurotropic factor both signal via the PI-3 kinase pathway, they have no effect on maintaining a latent infection. Lytic cycle viral gene expression can be detected within 15-20 hours after inhibiting the PI3-kinase pathway; surprisingly there are two peaks of viral mRNA expression [162, 163]. Viral RNA expression during the initial phase (Phase I) does not apparently require new viral protein synthesis and all classes of viral genes (IE, E, and L) are expressed. Phase I viral transcription is reduced prior to Phase II viral transcription, which begins between 25-30 hours after inhibiting PI-3 kinase. Phase II viral transcription resembles the cascade of viral gene expression that occurs in cultured cells, and VP16 is crucial for Phase II viral gene expression. VP16 protein expression during Phase I gene expression is primarily detected in the cytoplasm whereas it is localized to the nucleus during Phase II, which correlates with its ability to activate the normal lytic cycle of viral gene expression during Phase II. Although this model does not take into account the role that the immune system plays during reactivation from latency, it does have several distinct advantages with respect to examining the molecular mechanism by which HSV-1 reactivates from latency.

4.5. Natural host systems to examine reactivation from latency

The ability to study virus natural host interactions is attractive when examining the latency-reactivation cycle because it is clear that α-herpesvirinae subfamily members have co-evolved with their respective hosts. It is unlikely that one can recapitulate all of the complex virus-host interactions utilizing small animal models or *in vitro* models of latency. Thus, it is valuable to have natural host systems where the latency-reactivation cycle can be examined. Canine herpesvirus 1 (CHV-1) is an α-herpesvirinae subfamily member that consistently reactivates from latency following prednisone treatment [164, 165]. Although CHV-1 can be a significant problem in dogs, in particular puppies, the genome has not been sequenced and it can be difficult to grow in cultured cells. However, it has the potential to be an excellent model to provide insight into the mechanism by which α-herpesvirinae subfamily members reactivate from latency.

BHV-1, as other α-herpesvirinae subfamily members establishes latency in sensory neurons. Increased stress correlates with BHV-1 reactivation from latency, and consequently the virus is widespread in cattle [1, 2, 13, 166]. Administration of the synthetic corticosteroid DEX to latently infected calves or rabbits initiate BHV-1 reactivation from latency 100% of the time [1, 2, 32, 166-168]. Six hours after DEX treatment lytic cycle viral RNA expression is detected in neurons of latently infected calves [169, 170]. DEX treatment of latently infected calves induces apoptosis of T cells that persist in TG after infection [169]. T cells also persist in TG of humans or mice latently infected with HSV-1 [171-177] and promote maintenance of latency [178-183]. The viral regulatory proteins, bICP0 and VP16, can be detected in the same neuron within 90 minutes after calves latently infected with BHV-1 are treated with DEX [184]. Nearly all of the bICP0+ or VP16+ neurons express the glucocorticoid receptor (GR). Approximately 50% of TG sensory neurons express the GR [185] and the mineralocorticoid (MR) is also expressed in neurons [186]. I propose that DEX binds and activates the GR and/or MR, which subsequently stimulate lytic cycle viral transcription and reactivation from latency by direct and indirect mechanisms. By 6 hours after DEX treatment, other viral structural proteins, glycoprotein C and D, are detected in rare neurons [184].

Within 3 hours after latently infected calves are treated with DEX, 11 cellular genes are induced more than ten-fold in TG [101]. Pentraxin 3, a regulator of innate immunity and neuro-degeneration, is stimulated more than 30-fold by 3 or 6 hours after DEX treatment. Two transcription factors, promyelocytic leukemia zinc finger (PLZF) and Slug, are induced more than 15-fold three hours after DEX treatment. PLZF or Slug stimulates BHV-1 productive infection 20-fold or 5-fold, respectively, and Slug trans-activates the late glycoprotein C promoter more than 10-fold. Additional DEX-induced transcription factors, SPDEF, KLF15, KLF4, KLF6, and GATA6, stimulate productive infection and certain key viral promoters. The ability of DEX to consistently and rapidly induce reactivation from latency is an attractive model to study early events during reactivation from latency.

5. Stressful stimuli induce reactivation from latency by different signaling pathways

Although spontaneous reactivation from latency models have been valuable for identifying viral genes that regulate the latency-reactivation cycle, identifying events that initiate reactivation from latency require models where reactivation can be reproducibly induced. In general, heat stress and increased corticosteroids are the best external stimuli that can induce reactivation from latency in HSV-1 models of infection and BHV-1. Based on previously published studies, it appears that stimuli-specific signaling pathways initiate expression of key regulatory viral genes during early stages of reactivation from latency (Figure 4). A key point of this model is the prediction that disparate reactivation stimuli activate expression of different viral and cellular regulatory proteins during the initial stages of reactivation.

5.1. Regulation of reactivation from latency by heat stress

During heat stress-induced reactivation from latency, VP16 has been proposed to initiate reactivation from latency [63, 187] (Figure 4). Similar conclusions were made using the sympathetic neuronal culture system that is described above [163]. Since VP16 selectively activates IE gene expression [16, 188, 189], this model is logical because VP16 could initiate lytic cycle viral gene expression during early phases of reactivation from latency. However, the fact that the VP16 gene is a "true late" gene implies that heat stress-induced neuronal-specific transcription factors must trans-activate the VP16 promoter. Conversely, heat stress-induced cellular factors may transiently increase low levels of ICP0 or ICP4, which would subsequently selectively trans-activate the VP16 promoter. Currently, factors that stimulate VP16 promoter activity during heat stress-induced reactivation from latency have not been identified. The DEX-induced transcription factors that were initially discovered in bovine TG [101] and then found to stimulate HSV-1 ICP0 promoter activity [54] have no effect on VP16 promoter activity adding support to the hypothesis that heat stress induces other transcription factors that selectively trans-activate the VP16 promoter.

There is considerable information about how heat stress affects mammals, including humans and

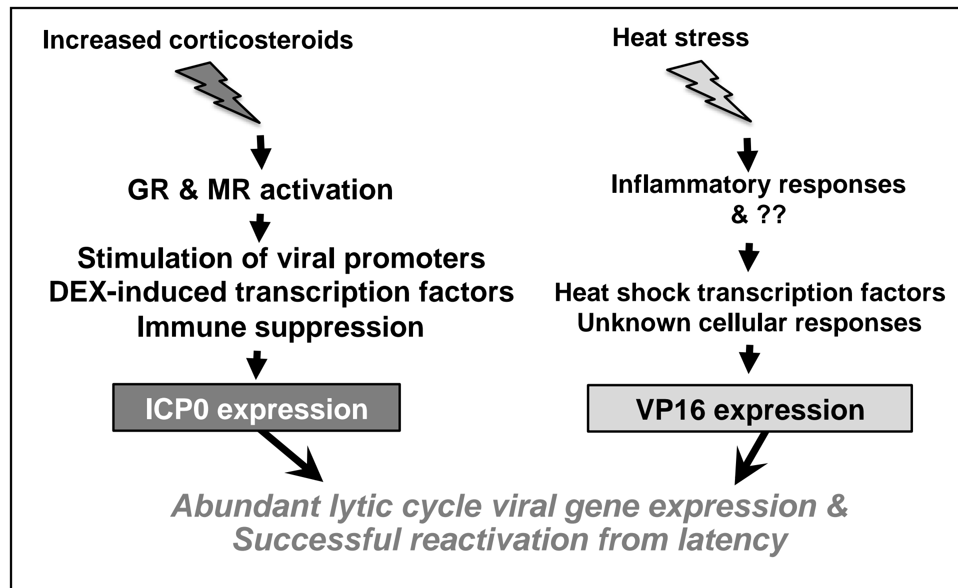

Figure 4. Schematic of putative steps leading to reactivation from latency. For details, see text.

mice. For example, heat stress is known to simulate fever and can also mimic heat stroke. Heat stroke is defined by a body temperature of more than 40 ºC and has many effects on the brain as well as causing a systemic inflammatory response, reviewed in [190]. Heat stroke has also been demonstrated to cause neuronal denaturation and necrosis in the brain when temperatures of the mouse reached 42 ºC regardless of cooling treatment [191]. In general, the fever response is part of an inflammatory response [192], which on the surface is quite different than the anti-inflammatory effects of corticosteroids, reviewed in [193, 194]. However, production of corticosteroids was reported to be crucial for heat stress-induced reactivation from latency [115]. This conclusion is based on the finding that cyanoketone, which blocks the production of active corticosterone [195], reduces heat stress-induced reactivation from latency. Cyanoketone may also have off-target effects that influence reactivation from latency. Interestingly, prophylactic corticosteroid treatment increases survival in experimental heat stroke in primates, in part by reducing lipopolysaccharide plasma levels [196] further suggesting heat stress is an inflammatory response. The question is whether placing mice in a 50 ml conical tube containing holes for ventilation and then incubating the mice in a 43 ºC water bath [114, 115] mimics the fever response or heat stress/stroke?

Regardless of whether heat stress-induced reactivation is the result of mimicking fever or heat stroke, the heat shock family of transcription factors, which regulates heat stress responses, is likely activated, reviewed in [197-199]. Heat shock transcription factors belong to the leucine zipper family of transcription factors. Nearly all heat shock responsive promoters contain one or more of the conserved inverted repeat sequence nGAAnnTTCnnGAAn (n denotes a less conserved nucleotide), which can be bound by a heat shock transcription factor. Although heat stress of cultured cells infected with HSV-1 selectively induced ICP0 expression [200], it is not known whether a heat shock transcription factor directly stimulates ICP0 promoter activity or any other viral promoter.

The fact that mice are also restrained during heat stress adds to the complexity of signals that stimulate reactivation from latency during heat stress-induced reactivation. For example, chronic restraint stress (12 hours in a well-ventilated 50 ml conical tube overnight for 4 consecutive days) of adult male C57BL/6J mice latently infected with the RE HSV-1 strain increases corticosteroid levels and reduces the number of

CD8+ T cells that can produce gamma-interferon, thus increasing the potential of reactivation from latency [201]. Conversely, BALB/c mice latently infected with the McKrae strain of HSV-1 do not significantly increase reactivation following the stress associated with restraint (16 hours in a well-ventilated 50 ml conical tube overnight) [202]. However, this study demonstrated that disruption of social hierarchy increased the incidence of reactivation as well as increasing corticosteroid levels. Clearly, mouse and viral strains may influence how stress restraint and other psychological stressors influence reactivation from latency. In summary, heat stress-induced reactivation in mice may reflect more than one stressor and multiple signaling pathways.

5.2. Regulation of reactivation from latency by corticosteroids

Several independent studies have provided evidence that corticosteroids accelerate or initiate reactivation from latency. For example, when TG from latently infected mice are explanted, reactivation from latency is accelerated by addition of DEX [153, 172] and initiation of viral transcription is mediated by ICP0 (Figure 4). As discussed above, other α-herpesvirinae subfamily members, canine herpesvirus type 1 [164] and BHV-1 [1, 2, 32, 166-168], consistently reactivate from latency following treatment with corticosteroids (prednisone or DEX, respectively).

Exogenous expression of ICP0, independent of other viral gene products, can initiate HSV-1 [203] or HSV-2 [204] reactivation from latency using an *in vitro* neuronal culture system. Furthermore, in the absence of VP16, ICP0 enhances the ability of transfected viral DNA to initiate productive infection in cell culture [205]. These observations suggest that reactivation stimuli activate the ICP0 promoter, which is an important event during explant-induced reactivation from latency (Figure 4). Consequently, it is not surprising that ICP0 promoter activity is stimulated by hyperthermic stress [200]. When TG from latently infected mice is explanted, reactivation from latency is accelerated by addition of DEX [153, 172] and initiation of viral transcription is mediated by ICP0. Several published studies support this model: 1) ICP0, independent of other viral gene products, initiates HSV-1 [203, 206, 207] or HSV-2 [204] reactivation from latency, 2) ICP0 RNA expression is rapidly detected following explant of TG [151], 3) ICP0 promoter activity is stimulated by DEX-inducible transcription factors [54], and 4) in the absence of VP16, ICP0 enhances the ability of transfected viral DNA to initiate productive infection in cell culture [205]. ICP4, but not mutant forms of ICP4 can also stimulate reactivation from latency using primary TG cell cultures prepared form mice latently infected with HSV-1 [203]. Considering ICP4 is required for productive infection and stimulates expression of early and late viral genes [208], it is not surprising that expression of the ICP4 protein would enhance reactivation from latency. In summary, it is unlikely that successful reactivation from latency (shedding of infectious virus following a reactivation stimulus) in humans can occur in the absence of ICP0, ICP4, or VP16 expression.

The glucocorticoid receptor (GR) or mineralocorticoid receptor (MR) dimer bound to a corticosteroid enters the nucleus and within minutes can have profound effects on chromatin confirmation as well as transcription. In general, nuclear GR or MR stimulates or inhibits transcription by binding consensus glucocorticoid response elements (GRE; 5'-GGTACANNNTGTTCT-3') [209, 210]. A GR or MR monomer can also stimulate transcription by binding to a GR ½-binding site [211, 212]. Within the HSV-1 and BHV-1 genomes, there are several potential GR or GR ½ binding sites in non-coding sequences (CJ, unpublished studies) suggesting viral promoters are directly stimulated by corticosteroids. The HSV-1 origin of replication in the U_L region (oriL) also contains a functional GR response element (GRE), and point mutations in the oriL GRE impair viral replication in mice [213, 214] providing support that corticosteroids directly influence viral DNA replication. As discussed above, DEX-inducible cellular transcripts trans-activated the BHV-1 and HSV-1 ICP0 promoters [54, 101]. Corticosteroids, in general, have a potent anti-inflammatory and immune-suppressive effect, in part by inactivating transcription factors (AP-1 and NF-κb) that stimulate expression of inflammatory cytokines reviewed in [193, 194].

Corticosteroids also induce apoptosis in certain lymphocyte subsets, which will interfere with immune responses. In summary, corticosteroids can affect reactivation from latency by at least three distinct mechanisms: 1) directly stimulating viral DNA replication, 2) directly or indirectly stimulating viral gene expression, and 3) interfering with immune responses.

CONCLUSIONS AND FUTURE STUDIES

Increased stress correlates with a higher incidence of reactivation from latency in humans [202, 215, 216]. Stress, in particular chronic stress, can interfere with immune functions, reviewed in [31], which is relevant to reactivation from latency. For example, it is well established that infiltration of CD8+ T cells and other lymphocytes into TG following infection with HSV-1 [172, 173, 217] or BHV-1 [169] occurs and these CD8+ T cells promote maintenance of latency infection by actively interfering with reactivation from latency [179, 181-183, 201, 218]. Interestingly, many stressors that stimulate reactivation from latency adversely affect immune functions. For example, psychological stress negatively affects CD8+ T cell control of maintaining HSV-1 latency in a mouse model of infection [201]. Stress, resulting in increased corticosteroids is also likely to stimulate reactivation from latency directly via the GR and MR trans-activating certain viral promoters and inducing cellular transcription factors. Recent studies identified cellular transcription factors that are induced by the synthetic transcription factor DEX [54, 101]. To date, there is no evidence that a HSV-1 or other α-herpesvirus promoters are trans-activated by an activated GR or MR. At the cellular or molecular level, it seems clear that different external stressors influence different cellular signaling pathways; consequently different viral promoters are stimulated during the early stages of reactivation from latency. This may explain why heat stress appears to be more dependent on VP16 during the initial stages of reactivation from latency [116] whereas ICP0 seems to be crucial for reactivation from latency following explant (see discussion in Section 5 and Figure 4).

With respect to reactivation from latency, there are many unresolved issues. For example, do different stressors initiate reactivation via unique signaling pathways and do these different stressors stimulate a subset of common cellular factors that promote reactivation from latency? Secondly, is the cascade of viral gene expression during reactivation the same as productive infection of cultured cells (immediate early → early → late)? Thirdly, do certain stress-induced cellular transcription factors stimulate reactivation from latency regardless of the stimulus? Fourth, if VP16 is responsible for initiating reactivation from latency, how is the VP16 promoter activated when VP16 is a late viral gene? Fifth, does the activated GR or MR directly stimulate viral transcription during initial stages of reactivation from latency? Sixth, what is the bottleneck that allows only a minor subset of neurons to produce infectious virus during reactivation from latency? Finally, do neurons that support successful reactivation from latency survive or do they die as a result of producing infectious virus? These questions are likely to be answered by using inducible models of reactivation from latency, heat stress induction, iontophoresis, and/or explant. The use of the natural host to study these complex virus host interactions may be necessary for addressing some of the unresolved issues associated with the latency-reactivation cycle. Thus, the ability of BHV-1 to consistently reactivate from latency following DEX treatment may be particularly useful. Finally, it is conceivable that different α-herpesvirinae subfamily members have developed virus-specific strategies to reactivate from latency, which can only be understood by taking a comparative approach.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

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