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Herpes simplex virus latency

Robin Lachmann

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are ubiquitous human pathogens. They share with other herpesviruses the ability to establish lifelong latent infection of the host. Periodic reactivation from latency is responsible for most of the clinical disease burden of HSV infection. This review focuses on what we have learned from molecular studies in model systems of HSV latency, and the implications these findings have for treating recurrent HSV disease.

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are human pathogens that have evolved with their hosts for the past 80 million years (Ref. 1). Like the other human herpesviruses, they are highly developed parasites capable of establishing lifelong infection: the majority of us are latently infected with several different herpesviruses. Periodic reactivation and shedding of infectious virus allows the infection of new hosts, and maintains high levels of viral infection within the population (Ref. 2).

HSV infection is endemic in all human populations. Epidemiological studies indicate that the prevalence of anti-HSV-1 antibodies increases with age (Ref. 3): in England and Wales seropositivity rates are 17–27% in those aged 1 to 14 years and 46% in the older population of blood donors. In some populations more than 90% of people have serological evidence of HSV-1 infection (Ref. 3). HSV-2 is generally less prevalent, although more than 80% of adults are seropositive in some populations from subSaharan Africa (Ref. 3). In the USA about 20% of adults are seropositive for HSV-2, although only 10% of these give any history of clinical symptoms (Ref. 4).

HSV, like other alphaherpesviruses, is neurotropic and establishes latency in primary sensory neurons. The majority of HSV-related morbidity is due to viral reactivation from neuronal latency, and the relationship between the virus and the sensory neuron is central to the pathogenesis of HSV infection.

HSV pathology

Oral and genital infections

The commonest sites of HSV infection are the oral and genital mucosae. The majority of primary oral infections are due to HSV-1 and result in a mild gingivostomatitis that often goes undiagnosed. In severe cases there can be ulceration in the mouth and pain can make swallowing difficult in some children. During primary infection, virus enters sensory nerve terminals and is transported retrogradely via axons to neuronal cell bodies in the trigeminal ganglion where latency is established (see below). Reactivation of the virus in the trigeminal ganglion seeds to the oral or nasal mucosae, most commonly at the vermillion border of the lip, to produce characteristic vesicles. Recurrence can be triggered by a multitude of different stimuli including physical trauma,

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sunlight and stress (Ref. 2). A minority of individuals seropositive for HSV-1 suffer with recurrent cold sores, although many more shed virus periodically in their saliva and this probably represents the major route for transmission to new hosts.

HSV-2 and, less commonly, HSV-1 can cause genital infections, leading to a sexually transmitted disease. Again, primary infections are often asymptomatic, although HSV-2 can cause proctitis or aseptic meningitis. After infection of the genital mucosa, latency is established in the sacral dorsal root ganglia. Genital infections recur more frequently than oral infections, as does asymptomatic shedding from the genital tract. The genital ulcers are more painful than oral cold sores and can be a major clinical problem, although they do eventually tend to remit spontaneously (Ref. 2).

Other infections

Skin

HSV in infected secretions can infect damaged skin on any part of the body, giving rise to a crop of vesicles (e.g. herpetic whitlow, scrum pox). These primary cutaneous lesions also lead to the establishment of latency in the dorsal root ganglia that innervate the site of infection, and patients can suffer from periodic recurrence anywhere in the relevant dermatome. If HSV infects inflamed skin in patients with atopic dermatitis, it is able to spread rapidly over large areas and can be associated with severe systemic illness (eczema herpeticorum) (Ref. 2).

Eye

Herpetic keratitis has an incidence of about 8 cases per 100 000 population per year and is a major cause of corneal blindness, with unilateral visual impairment occurring in at least a third of patients with recurrent episodes (Ref. 5). The primary infection causes an acute, bilateral keratoconjunctivitis that resolves without causing corneal damage, but recurrent disease, which is unilateral, causes dendritic ulcers that can lead to permanent corneal scarring (Ref. 2).

Central nervous system

HSV replication in the brain causes encephalitis (Ref. 2). This is a life-threatening disease with a high mortality that causes permanent neurological damage in those who survive. Herpes encephalitis can be a manifestation of primary infection or secondary infection, and it is unclear how the virus enters the central nervous system. Fortunately, the condition is rare (with an incidence of approximately 1 in 200 000 in the USA) and, if diagnosed at an early stage, responds to treatment with antiviral agents; these have significantly reduced the associated mortality and morbidity.

There is also epidemiological evidence that the presence of HSV-1 DNA in the brain might be associated with Alzheimer's disease, although no molecular mechanism for such a link has been proposed (Refs 6, 7, 8).

Congenital and neonatal infection

Generalised HSV infection of the neonate has a very high mortality (Ref. 2). Infection is often acquired during passage through the birth canal, but can also be acquired in utero. Caesarian section has been used in mothers with genital ulcers in an attempt to minimise the risks of peripartum transmission.

Lytic infection

The lytic pathway of HSV infection (summarised in Figure 1; for an animation see http://www.expertreviews.org/99000381h.htm) has been extensively studied in tissue culture cells and is characterised by the highly regulated sequential expression of three temporal classes of viral gene products (reviewed in Refs 9, 10). The first viral genes to be transcribed are the immediate early (IE) genes. Efficient establishment of IE gene expression requires the presence of the virion transactivator protein VP16, which binds to a consensus sequence upstream of the five IE promoters and recruits cellular transcription factors (Ref. 11). Four of these five genes – IE1 (ICP0), IE2 (ICP27), IE3 (ICP4) and IE4 (ICP22) – are involved in the regulation of viral gene expression. IE5 (ICP47) has a role in immune evasion (Ref. 12).

Subsequent early (E) and late (L) gene expression is dependent on the synthesis of IE gene products; if cells are infected in the presence of inhibitors of protein synthesis (e.g. cycloheximide), then only the five IE genes are transcribed (Ref. 13). Of the E gene products, seven are required for replication of the viral DNA (Refs 14, 15) and others, such as those for thymidine kinase (TK) and ribonucleotide reductase, are involved in modifying the cellular milieu to support rapid DNA synthesis. L gene

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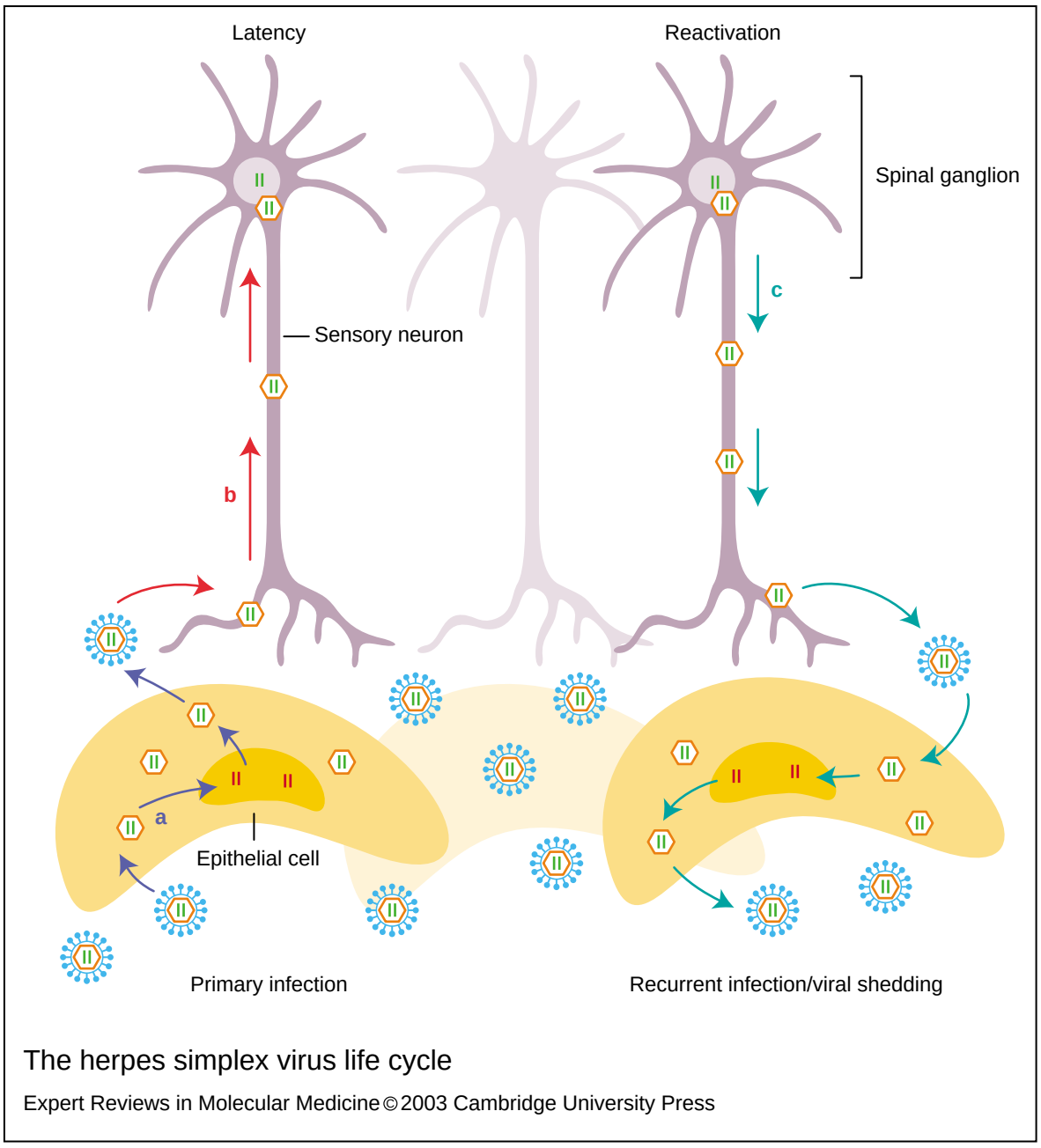


Figure 1. The herpes simplex virus life cycle. (a) Herpes simplex virus (HSV) is shown undergoing the lytic cycle (entry, uncoating, viral transcription and DNA replication in the nucleus, particle assembly, exit from the cell) in epithelial cells of the skin to cause a primary infection. (b) Some virus enters the sensory neuron terminals and travels retrogradely to the nucleus where it establishes latency. (c) Periodic reactivation results in anterograde transport of viral particles, shedding from the neuron, and re-infection of epithelial cells, which leads to asymptomatic shedding or recurrent lesions.

expression is dependent, to varying degrees, on prior synthesis of viral DNA (Ref. 16). The products of the L genes are mostly structural components of the virion.

Viral protein synthesis occurs in the cytoplasm, but the nucleocapsids are assembled within the nucleus. These nucleocapsids recognise the nascent viral genomes, which are cleaved into monomers as they are packaged (Ref. 17). The completed nucleocapsids exit the nucleus by

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budding through the nuclear membrane. The virus then exits the cell by traversing several membrane-bound organelles, where it acquires its mature envelope and glycoproteins (Ref. 18). Eventual cell lysis is the inevitable outcome of lytic infection with HSV-1 in tissue culture cells.

HSV latency

Latency in humans

The link between surgical procedures on the trigeminal ganglion and reactivation of herpetic infection, first described by Cushing (Ref. 19), and observations by Goodpasture that recurrent cold sores in humans occurred at the same anatomical site but that no virus could be cultured from the skin between attacks (Ref. 20), led to the the hypothesis that HSV established a latent infection within sensory neurons. Viral DNA was first demonstrated in the trigeminal ganglia of cadavers, which exhibit no evidence of active disease by Southern blotting (Ref. 21). Recent work using polymerase chain reaction (PCR)-based methods to detect viral DNA in post-mortem tissue has shown that the latent viral genomes are present in neurons and not satellite cells (Ref. 22). These investigators found latent viral genomes in about 3% of sensory neurons in positive trigeminal ganglia and calculated that the average copy number of latent genomes per cell was 16. Further characterisation of this latent infection in humans has been limited, but it has been demonstrated that, although no viral antigen can be detected in, nor virus isolated from, freshly dissected sensory ganglia, infectious virus is produced after these tissues have been maintained in tissue culture for a few days (Refs 23, 24, 25, 26). This reservoir of viral DNA within sensory neurons does, therefore, appear to be a potential source for viral reactivation and recurrent lesions.

Animal models of latency

Detailed investigation of HSV latency has required the development of models of infection. Although humans are the only natural host of HSV infection, experimental infection of a wide range of animals is possible.

HSV-1 infection has been studied mostly in mouse and rabbit models. In the mouse, infection of the footpad, eye, ear or flank leads to replication at the local epithelial site and axonal transport of virus to the relevant sensory ganglia. Limited replication occurs in the ganglion, followed by the establishment of a latent infection, but spontaneous reactivation occurs only rarely, if at all, in the mouse (Ref. 27) (Fig. 2). Latently infected murine neurons might therefore not share the same 'functionality' as their human counterparts.

The other commonly used model of HSV-1 infection is the rabbit eye model. Here, infection of the cornea allows latency to be established in the trigeminal ganglion, following which, although there is no spontaneous recurrence of disease, virus can periodically be cultured from the animal's tears. This situation might be analogous to the asymptomatic shedding of HSV-1 and HSV-2 that occurs in infected humans (Refs 28, 29).

Although these models bear some resemblance to human disease, no animal has been found where experimental infection with HSV-1 leads to periodic, spontaneous recurrence of peripheral lesions. The only model that reproduces the clinical course of a human HSV infection is genital infection of guinea pigs with HSV-2 (Ref. 30), but this model has not been amenable to detailed molecular study.

The nature of the latent genome

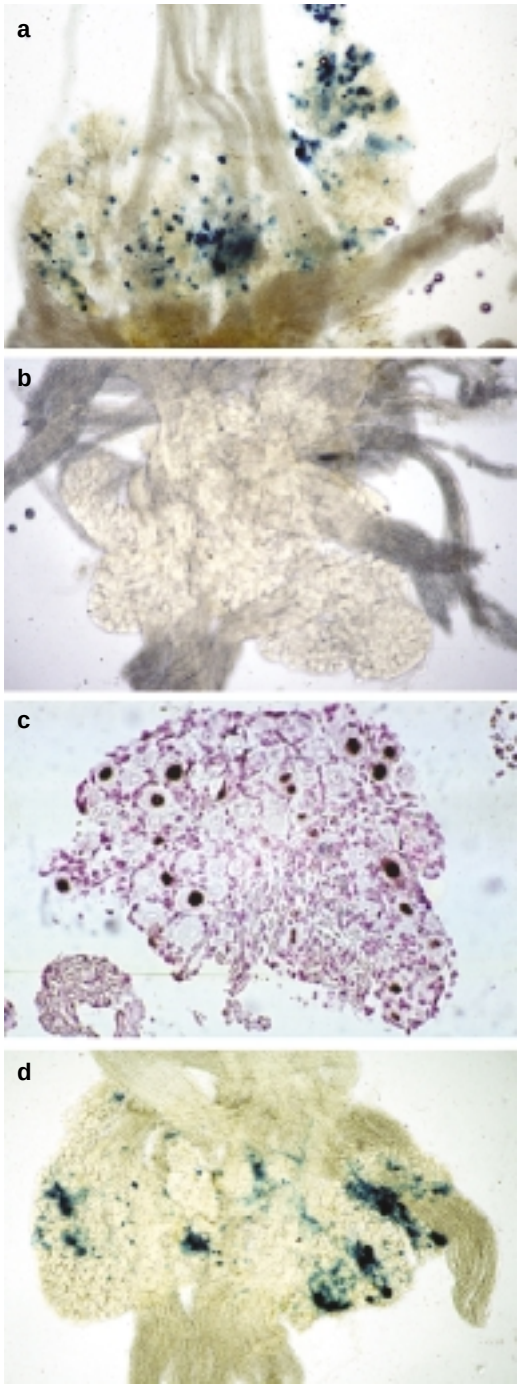
Early studies of HSV latency in mice demonstrated that the virus was able to establish a truly latent infection with the persistence of viral DNA without evidence of any viral antigen in latently infected tissue (Ref. 31). The DNA isolated from latently infected ganglia of both mice and humans differed from that isolated from virions in that, after restriction digestion and Southern blotting, it lacked terminal fragments and seemed to exist in an endless form in which the genome termini had fused to form circles or long concatamers (Refs 21, 32). When DNA from latently infected mice was fractionated on a caesium chloride density gradient, the viral sequences could be separated from chromosomal DNA, indicating that the genome persists as an episomal element (Ref. 33), which has a nucleosomal structure similar to that of cellular chromatin (Ref. 34).

Latent-phase transcription

Although no viral proteins have been consistently detected in latently infected tissues, there is continuing transcription from the viral genome (Ref. 35). Analysis of latently infected tissue by northern blotting and in situ hybridisation (ISH) using strand-specific probes has shown that a family of nuclear RNA species, called the latency-

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Gene expression during latency establishment and reactivation

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Figure 2. Gene expression during latency establishment and reactivation *(see next column for legend).*

Figure 2. Gene expression during latency establishment and reactivation. Mice were infected by inoculation of the ear with a recombinant herpes simplex virus type 1 containing the *lacZ* reporter gene under transcriptional control of the viral IE1 promoter. Cervical dorsal root ganglia were harvested at different times post-inoculation and either stained for β-galactosidase (β-gal) activity using X-gal or processed for in situ hybridisation. (a) At 4 days post-inoculation there is abundant IE1-promoter-driven β-gal expression (blue cells) in the dorsal root ganglia. (b) At 31 days post-inoculation there is no detectable β-gal expression as a result of transcriptional repression of the viral genome. (c) If ISH is performed using a LAT-specific ribroprobe, latently infected neurons can readily be detected in ganglia harvested 31 days post-inoculation. (d) If ganglia are explanted 31 days post-inoculation and incubated at 37°C for 48 h prior to X-gal staining, reactivation of viral lytic cycle gene expression can be detected. For further experimental details see Ref. 56.

associated transcripts (LATs), which overlap the IE1 gene but are encoded on the opposite strand, are transcribed in a proportion of latently infected neurons (Refs 36, 37, 38) (Fig. 3).

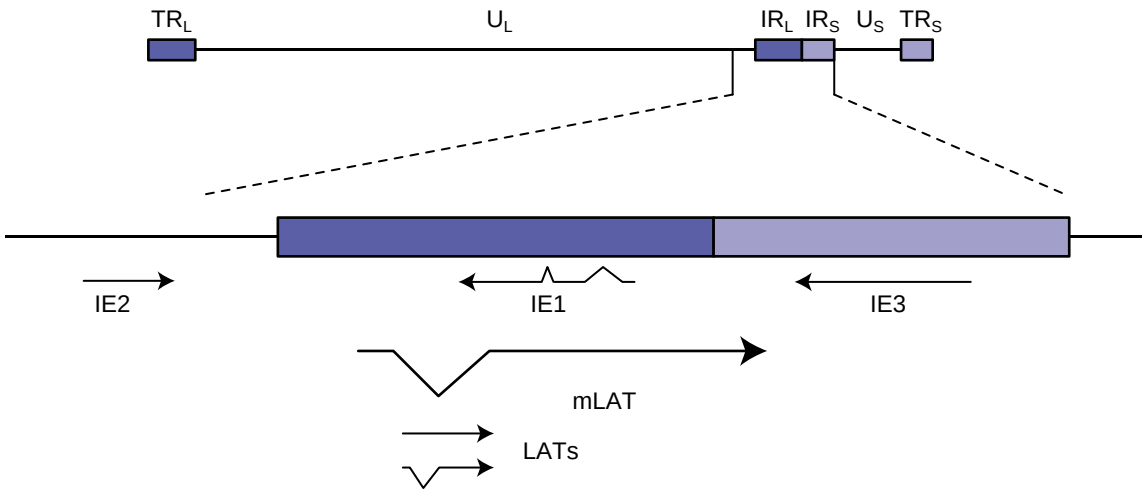
The primary LAT transcript, termed minor LAT because of its low abundance, is a polyadenylated species of about 8.3 kb (Refs 39, 40). ISH has shown that this species is localised to discrete intranuclear foci, which might represent sites of transcription from latent viral genomes (Ref. 41). The major LATs – stable introns of 1.5 kb and 2 kb that are abundant throughout the nucleus – are spliced from this primary transcript (Refs 36, 42).

The function of the LATs is not clear. Although LAT mutants are able to establish, maintain and reactivate from latency, deletion mutants that cannot express the LATs do appear to be less efficient in establishing latency in both mouse and rabbit models (Refs 43, 44). This function might relate to an anti-apoptotic function of the LATs that prevents neuronal death during early infection or to an ability of the LATs to downregulate lytic cycle gene expression in neurons, thus favouring the establishment of latency (reviewed in Ref. 45). LATs have also been ascribed a role in reactivation (Refs 46, 47, 48, 49), but some of these observations may be secondary to decreased efficiency of latency establishment. Although major LAT contains two ORFs, these are not conserved between HSV-1 and HSV-2, which otherwise show very high conservation of their

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Organisation of the herpes simplex virus type 1 genome, showing the origin of latency-associated transcripts

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Figure 3. Organisation of the herpes simplex virus type 1 genome, showing the origin of latency-associated transcripts. The gene for the latency-associated transcripts (LATs) is diploid and located in the repeat regions flanking the unique long (U_L) sequence of the genome (double-stranded DNA) close to the IE1, IE2 and IE3 genes; the minor (primary) latency associated transcript (mLAT; ~8.3 kb) is transcribed from the opposite strand to IE1. Major LATs are introns of ~1.5 kb and ~2 kb that are spliced from mLAT as indicated in the figure. Abbreviations: IR, internal repeat; TR, terminal repeat; U_L, unique long sequence; U_S, unique short sequence.

gene products (Ref. 50), and there is no evidence that they are expressed in vivo. It therefore seems likely that whatever the function of the LATs is, it is intrinsic to the RNA transcripts.

The establishment of latency

Historically, the only way to assess the latency competence of a mutant virus was to measure its ability to reactivate in an animal model. Although not all latently infected neurons transcribe detectable levels of LATs (Ref. 51), the detection of LATs by ISH (Fig. 2c), in combination with measurement of latent viral genomes, has made it possible to dissect out the events involved in the establishment of latency from those involved in reactivation. By studying viral mutants it has been possible to start to define where the lytic and latent pathways of HSV infection diverge.

Several viruses containing mutations within the VP16 gene and/or one or more of the IE genes have been described. Such viruses are unable to initiate lytic cycle infection in noncomplementing cells in tissue culture (Refs 52, 53). However, a number of such mutants can efficiently establish latent infection in neurons in vivo (Refs 54, 55). These data suggest that latency can be established in the absence of any lytic cycle gene expression, and might represent a 'default' pathway that occurs following virus entry into a cell that is nonpermissive for the initiation of lytic cycle gene expression. Support for such a default model of latency has come from studies using fully replication-competent HSV-1 in mouse models. During latency, LAT-expressing neurons can be found in sensory ganglia in which there had been no detectable lytic cycle gene expression during the establishment phase of infection (Refs 56, 57). Furthermore, during acute infection of ganglia innervating the site of inoculation, two separate populations of neurons have been identified – one expressing lytic cycle genes and the other expressing only the LATs (Refs 58, 59), suggesting that the lytic and latent pathways of gene expression can diverge from each other immediately upon infection of the neuron.

Studies with replication-competent viruses, however, have indicated that viral replication is required for the efficient establishment of latency.

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After infection with wild-type virus, the copy number of viral genomes per latently infected cell is highly variable, ranging from 10 to 1000 (Refs 60, 61, 62, 63). This variation in copy number could simply relate to the number of input genomes and reflect the efficiency of viral replication either at the periphery or in the ganglion. Alternatively, it is possible that neurons could support limited viral gene expression and amplification of viral DNA prior to the establishment of latency, although there is currently no evidence from animal studies to support this hypothesis.

The only evidence suggesting that lytic and latent cycle gene expression are not mutually exclusive in neurons comes from an in vitro model of latency. It has been shown that efficient establishment of latency in cultured sensory neurons requires expression of ICP0 (the IE1 gene product), even when neurons are infected at high multiplicity (Ref. 64). The defect in establishment shown by an IE1$^-$ virus could be corrected by providing ICP0 in trans from a recombinant adenovirus. How these observations relate to latency establishment in humans or animal models is not clear, however, as it is only possible to establish latency in these neuronal cultures by blocking the lytic cycle with acyclovir. Without acyclovir there is unrestricted viral replication, which results in the death of all the cells in the cultures. This suggests that mechanisms that limit acute phase viral replication in the intact ganglion (e.g. the immune response) might have a role to play in latency establishment.

Recent studies of infected fibroblasts in tissue culture, using a replication-defective mutant unable to express IE gene products, have shown that a fraction of viral genomes circularise and can then persist in a transcriptionally repressed state resembling that of the latent genome in neurons (Ref. 65). Expression of ICP0 inhibited the formation of circular genomes in these conditions and circular genomes were never seen in productive infections with wild-type virus. These data suggest that failure of ICP0 expression and circularisation of the genome might represent the first committed step on the pathway to viral latency.

Reactivation

Factors implicated in reactivation

Reactivation from latency is an essential element of the herpesvirus life cycle, allowing spread of the virus to new hosts. With HSV, reactivation is responsible for recurrent clinical symptoms as well as viral spread, and the prevention of reactivation is an important therapeutic goal.

In latently infected patients, the events triggering reactivation of HSV-1 and the appearance of recurrent cold sores are not well understood. Immunosupression, febrile illnesses, exposure of the skin of the lips to UV irradiation and 'stress' have all been reported to precipitate recurrence (Ref. 2), but the molecular biology of reactivation cannot be studied in humans.

Both the mouse and rabbit models of HSV-1 infection allow reactivation to be studied, but it is not clear how reactivation induced by artificial stimuli, such as explantation of latently infected murine ganglia (Fig. 2d), heat stressing mice or iontopheresis of adrenaline into the rabbit eye, are biologically related to the spontaneous reactivation seen in humans. Recurrence induced by skin trauma or UV irradiation might be more physiological (Ref. 66).

Some of the complexities of animal model systems can be avoided by using tissue culture models of latency. The initial observations that latent HSV could be reactivated by neurectomy led to the suggestion that the removal of some neurotrophic factor provided by the peripheral target might result in reactivation of the virus (Ref. 67). Wilcox and colleagues have shown that, in their in vitro model, neuronal latency is dependent on nerve growth factor (NGF): withdrawal of NGF leads to reactivation of productive infection within 24 h (Ref. 68). Biologically, it makes sense for the virus to reactivate from a neuron that has been deprived of trophic support and might therefore die, but it seems unlikely that NGF withdrawal is the sole mechanism leading to spontaneous reactivation events. Using the same model of latency, these investigators went on to demonstrate that activation of either cAMP- or protein-kinase-C-dependent second messenger pathways could result in reactivation of latent infection (Ref. 69).

Halford et al. have established cultures from latently infected murine trigeminal ganglia. By dissociating the ganglia in the presence of inhibitors of viral DNA synthesis, they are able to limit reactivation at explantation, and maintain LAT-expressing, latently infected neurons in culture (Ref. 70). In this in vitro system, heat stressing the cultures led to reactivation of virus. Activation of the cAMP pathway by using pharmacological agents did not result in

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reactivation, but corticosteroid treatment did.

Molecular basis of reactivation

Thus, activation of various second messenger systems in neurons that have been exposed to 'stressful' stimuli might lead to viral reactivation. How do these changes in the intracellular milieu result in the switch from latent to lytic cycle viral gene expression?

It is clear that the initiation of reactivation from latency cannot be exactly analogous to initiation of lytic infection in tissue culture. The physical state of the latent genome is distinct from that of the genome extruded from the nucleocapsid into the nucleus of the acutely infected cell in that it exists in an endless form (probably a circle) that is nucleosomally associated. The latent genome is transcriptionally repressed, and there is no VP16 present in the latently infected neuron to transactivate the IE gene promoters. Indeed, a VP16 mutant virus can reactivate from latency (Ref. 71), so VP16 is clearly not required. How is the transcriptional repression of the latent genome overcome, and is IE gene expression the first event in viral reactivation?

IE1 mutant viruses show very inefficient reactivation from latency in animal models (Refs 72, 73). Providing ICP0 in trans induces reactivation of HSV-1 from cultured latently infected trigeminal ganglion neurons (Ref. 74). ICP0 can also derepress transcription from quiescent viral genomes in tissue culture models of latency (Refs 53, 75). Expression of ICP0 has been linked to stimuli that provoke reactivation in vivo: in a transgenic mouse expressing β-galactosidase from the ICP0 promoter, stimuli such as UV irradiation and hyperthermic stress, which lead to reactivation of latent virus, stimulate expression of this reporter gene in trigeminal ganglion neurons (Ref. 76).

It seems likely, therefore, that expression of ICP0 has a crucial role to play in reactivation. What might its function be? ICP0 is a transactivator of viral gene expression but it is not a classical DNA-binding transcription factor (Ref. 77). Rather, ICP0 is an E3 ubiquitin ligase, which, by degrading certain key proteins, leads to the destruction of ND10 (PML) bodies in the cell nucleus (Ref. 78). ND10 bodies are nuclear accumulations of proteins that are upregulated by interferon. Although their function is not fully understood, ND10 bodies seem to have an important role to play in the replication of DNA viruses (Refs 79, 80). A number of transcription factors are associated with ND10 domains and it has been suggested that they are involved in transcriptional control (Refs 81, 82).

Although parental HSV genomes are localised to ND10 domains early during productive infection, there is no direct evidence that this is the site of the latent genome. However, as mentioned above, ISH has indicated that the primary LAT transcript is localised to discrete domains within the nucleus, whose distribution resembles that of ND10s (Ref. 41), and these might represent sites of transcription from the latent viral genome. Perhaps ICP0 causes changes in the ND10 domains that favour lytic rather than latent transcription from the viral genome. Changes in the transcriptional milieu of ND10 domains would then be the mechanism of viral reactivation.

Reactivation in both tissue culture and explant systems leads to the rapid spread of viral infection throughout the culture or explanted ganglion. This clearly does not parallel the situation in vivo, where viral replication in the ganglion is highly restricted, with little evidence of neuronal loss (Ref. 83). It is postulated that this restriction of viral infection within the ganglion is mediated by the immune system, but, although immunosuppression can lead to reactivations, these are not associated with high levels of viral replication within the nervous system (Refs 84, 85). Recent work using a mouse eye model of infection has shown that latently infected ganglia contain activated $CD8^+$ T cells that specifically recognise HSV glycoprotein B (Ref. 86). The authors propose that these T cells might function to suppress viral reactivation, but an alternative explanation is that they are a response to the sporadic neurons expressing lytic viral transcripts, presumably as the result of a reactivation event, that can be detected in latently infected murine ganglia (Ref. 87).

In the rabbit eye model, although transcription of lytic cycle genes can be detected in trigeminal ganglia that have been dissected after iontopheresis of adrenaline into the eye, no net increase of ganglionic viral DNA can be detected in association with the reactivation event (Ref. 88). Furthermore, levels of viral DNA and numbers of LAT-expressing neurons in latently infected rabbit trigeminal ganglia do not change significantly over time, despite the occurrence of spontaneous reactivations and recurrences

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(Ref. 89). The events that follow reactivation in vivo are therefore very different from those seen ex vivo, and they must diverge from each other at a very early stage in the reactivation process.

Treatment of HSV infection

Antiviral drugs

The acyclic purine nucleoside analogue acyclovir has been the mainstay of HSV antiviral chemotherapy (Ref. 90). Acyclovir can be converted to its active form, acyclovir triphosphate, only by the sequential action of the viral TK and cellular kinases. Acyclovir triphosphate is incorporated by the viral DNA polymerase into nascent viral genomes where it acts as a chain terminator and inhibits viral replication. Acyclovir can be given topically, orally or by intravenous infusion. If given early in infection, acyclovir can shorten episodes of recurrent oral and genital disease, and daily dosing can reduce the frequency of recurrences. Topical acyclovir is effective in treating eye infections and, given intravenously, acyclovir can be life saving in HSV encephalitis.

Because of its low bioavailability, oral acyclovir must be taken every four hours and this can lead to problems with compliance. Valacyclovir and famciclovir are oral prodrugs of acyclovir that have more favourable pharmacokinetics and can be given less frequently. Penciclovir has a similar mode of action to acyclovir. Cidofovir is a nucleoside analogue that targets the viral DNA polymerase without the need for prior phosphorylation by the viral TK (Refs 90, 91).

Acyclovir resistance is seen only rarely in the immunocompetent, even in those on long-term prophylaxis to reduce the frequency of recurrent bouts of infection, but is more common in the immunocompromised. Resistance can result from mutations in either the TK or the viral DNA polymerase. In these cases, foscarnet, a pyrophosphate analogue that competitively binds DNA polymerase and prevents chain elongation, can be used.

These currently available agents all target the viral DNA polymerase. There are many other stages of the virus life cycle that are potential targets for drug therapy, such as viral entry, transcription and virion assembly, and several new compounds with activity against HSV replication in tissue culture are being developed (reviewed in Ref. 92).

Vaccination

If it were possible to intervene with antiviral drugs early in primary infection it might be possible to interfere with the establishment of latency and hence prevent recurrent disease. This is not a realistic prospect, however, as primary infection is normally asymptomatic and rarely diagnosed at the time. An alternative approach would be to vaccinate, although it is not clear that this would be effective in preventing primary infection as it is known that patients who are immune to HSV-1 can still undergo a primary infection with HSV-2 despite the fact that they have crossreacting serum antibodies that neutralise HSV-2 in vitro. Even if it were not possible to prevent primary infection, however, postexposure vaccination might be able to prevent recurrent disease (Ref. 93). Several different attenuated, recombinant and subunit vaccines have undergone clinical trials and some results have been promising (Ref. 93). At present, however, no products have been licensed for clinical use.

Clinical implications/applications

Currently available drugs are effective against active HSV infection, and long-term prophylaxis can reduce the incidence of recurrent symptoms in at least some patients. If antivirals were used in primary infection, they might impact on the establishment of latency and be able to reduce the probability of a patient suffering recurrent episodes but, as primary infection is asymptomatic in the vast majority of cases, this is not a practicable approach.

The ideal approach to controlling recurrent HSV infections would be to eradicate latent viral genomes. This would require therapeutic targeting of a process involved in the maintenance of latency. The only viral candidate for such a process would be the LATs. We know that LAT expression is not essential for latency in animal models, but it is possible that LATs might have a role to play in human infection, perhaps through their anti-apoptotic function. At present we do not understand how the LATs achieve any of their described functions, and therapeutic intervention targeting LATs is not possible. It is not known whether there are cellular processes actively involved in maintenance of the latent viral genome. In any case, if HSV is latent in 3% of trigeminal ganglion sensory neurons (Ref. 22), the eradication of cells containing latent viral

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genomes might not be desirable.

The most attractive way to prevent recurrent disease would be to prevent viral reactivation. Although our understanding of reactivation is incomplete, it seems that expression of the viral IE genes, especially ICP0, is a crucial step that could be specifically targeted. Antiviral agents that inhibit HSV IE gene expression have been reported (Refs 94, 95). Alternatively, if we understood more about the processes involved in transcriptional repression of the latent genome, it might be possible to 'stabilise' the latent viral DNA and prevent reactivation by maintaining tight repression. Because we cannot predict when reactivation will occur, any therapy aimed at reactivation would have to be given prophylactically.

Outstanding research questions

What is the function of the LATs? Intuitively, it would seem that LATs are central to the relationship between the virus and the sensory neuron but, although they were first described 15 years ago, they are still the subject of controversy. They have been shown to suppress IE gene expression in vitro, to have anti-apoptotic activity in tissue culture and in infected ganglia, and to contribute to the efficiency of latency establishment and reactivation. LATs might therefore be multifunctional, but none of these functions is essential in the animal models presently available; viruses that are unable to synthesise LATs can still establish, maintain and reactivate from latency.

What is the nature of the lytic–latent switch? Can neurons sustain some IE gene expression prior to the establishment of latency or does latency occur by a default pathway?

What are the early events in reactivation? Does transcriptional derepression of the viral genome follow selective expression of ICP0 or is a cellular factor (perhaps homologous to ICP0) responsible?

What is the fate of the latently infected neuron after reactivation? Does reactivation inevitably lead to neuronal death or can neurons survive limited productive cycle gene expression and re-establish latency?

Many laboratories continue to investigate these issues in different in vitro and in vivo models of latency. Perhaps the most difficult question of all is how do the various, not always compatible, findings that come out of these model systems relate to HSV latency in humans, the only species in which natural HSV infection occurs.

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Further reading, resources and contacts

An introduction to HSV biology is given at the homepage of Edward Wagner (School of Biological Sciences, University of California, Irvine, USA):

http://darwin.bio.uci.edu/~faculty/wagner/

The International Herpes Management Forum website discusses clinical management of herpesvirus infections:

http://www.ihmf.org/

'All the virology on the WWW' provides links to a range of virology-related sites and a virology picture index:

http://www.virology.net/

Features associated with this article

Figures

Figure 1. The herpes simplex virus life cycle.
Figure 2. Gene expression during latency establishment and reactivation.
Figure 3. Organisation of the herpes simplex virus type 1 genome, showing the origin of latency-associated transcripts.

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