Review

Development of new antivirals for herpesviruses

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The long-term treatment of herpesvirus infections with current antivirals in immunocompromised hosts leads to the development of drug-resistant viruses. Because nearly all currently available antivirals finally target viral DNA polymerase, virus resistant to one drug often shows cross-resistance to other drugs. In addition, nearly all the antivirals show various kinds of side effects or poor bioavailability. This evidence highlights the need for developing new antivirals for herpesviruses that have the different viral targets. Recently, high-throughput screening of large compound collections for inhibiting specific viral enzymes, or in vitro culture assay, has identified several new antivirals that target different viral proteins. These include the inhibitors of helicase/primase complex, terminase complex, portal protein and UL97 protein kinase. In addition, non-nucleoside inhibitors for viral DNA polymerase have been also developed. This review will focus on these new compounds that directly inhibit viral replication.

Keywords: human herpesvirus, HHV, herpes simplex virus, HSV, nucleoside analogue, human cytomegalovirus, HCMV

Introduction

The human herpesviruses are a family of double-stranded DNA viruses that cause a variety of clinically significant diseases (Table 1). The most remarkable characteristics of herpesvirus infections are their ability to establish lifelong latency in the hosts and to reactivate from the latency, leading to recurrent episodes of diseases (Griffiths, 1996). The human herpesviruses are subdivided into alpha, beta and gamma subfamilies. This subdivision is based mainly on sequence data, including gene complement and gene order, and on biological characteristics such as host range, viral life cycle and the cell type in which a virus establishes and reactivates from latency.

The alphaherpesviruses, consisting of herpes simplex virus type 1 (HSV-1), type 2 (HSV-2) and varicella-zoster virus (VZV), infect mucocutaneous epithelial cells and establish latency in sensory ganglions (Whitley & Roizman, 2001). HSV-1 causes gingivostomatitis, cold sores, keratoconjunctivitis and encephalitis, while HSV-2 primarily causes genital herpes. The primary VZV infection causes chickenpox, while the reactivation of VZV from the ganglion results in herpes zoster. The betaherpesviruses, consisting of human cytomegalovirus (HCMV) and human herpesvirus type 6 (HHV-6) and type 7 (HHV-7), infect and establish latency in T lymphocytes and the cells of monocyte/macrophage lineage (Frenkel & W yatt, 1992; Zhuravskaya et al., 1997; Black & Pellett, 1999). Although primary HCMV infection is usually asymptomatic in healthy people, it causes morbidity and mortality in the foetus with immature immunity and in immunocompromised hosts, such as patients with transplantation, cancer or acquired immunodeficiency syndrome (AIDS) (Sissons & Carmichael, 2002). Both HHV-6 and HHV-7 are the causative agents of roseola infantum. Although the direct evidence is not clear, HHV-6 may be involved in opportunistic disease after organ transplantation.

The gammaherpesviruses, consisting of Epstein-Barr virus (EBV) and human herpesvirus type 8 (HHV-8), infect and establish latency in lymphocytes. EBV causes self-limiting infectious mononucleosis and involves in human malignancies such as Burkitt’s lymphoma, nasopharyngeal carcinoma, opportunistic B-cell lymphoma and others. HHV-8 is strongly associated with Kaposi’s sarcoma, primary effusion B-cell lymphoma and multicentric Castleman’s lymphoma in AIDS patients (Ensoli et al., 2001).

Current chemotherapy for herpesviruses

Herpesviruses establish latent infections in their hosts that recur during immunosuppression; accordingly, inhibiting viral replication is not sufficient to eradicate herpesvirus infections (Visalli & van Zeijl, 2003; Coen & Schaffer, 2003). Latent virus cannot be eliminated from the host. At present, we are limited to suppressing reactivation using the currently available antivirals. Human herpesviruses have
large genomes ranging in size from 125–235 kbp and these large genomes encode more than 50 gene products that are essential for viral replication (Coen & Shaffer, 2003). Although any viral protein essential for viral replication is a potential target, nearly all currently available drugs for herpesviruses are primarily inhibitors of viral DNA polymerase (Figure 1). These drugs are divided into three chemical groups: nucleoside analogues, nucleoside phosphonate (nucleotide) analogues and pyrophosphate analogues (Visalle & van Zeijl, 2003). The first group includes acyclovir (ACV), ganciclovir (GCV), penciclovir (PCV), brivudin (BVDU); the second group includes cidofovir (CDV); and the third group includes foscarnet (PFA).

Nucleoside and nucleotide analogues are substrates for the viral DNA polymerase. The nucleoside analogues should be converted to triphosphate active form by phosphorylation in the infected cells. The first monophosphorylation of analogues such as ACV, GCV, PCV and BVDU is selectively performed by viral enzymes. These enzymes include thymidine kinase (TK) for HSV-1, HSV-2 and VZV and UL 97 protein kinase for HCMV (Elion, 1983; Littler et al., 1992). Subsequently, the di- and the tri-phosphorylation of all nucleoside analogues, except for BVDU, are catalysed by cellular enzymes. The di-phosphorylation of BVDU depends on viral TK. The tri-phosphorylated active forms compete with the binding of normal triphosphates (dNTPs) as a substrsate for viral DNA polymerase. Incorporation of nucleoside analogues into nascent DNA blocks DNA elongation. Because the nucleoside analogues, ACV, GCV and PCV have poor bioavailability, the bioavailable prodrugs of these analogues, valacyclovir, valganciclovir and famciclovir have been developed respectively. The oral administration of these prodrugs results in the higher plasma levels and is very useful and convenient for the treatments in HSV, VZV and HCMV infections. Therefore, ACV, GCV, PCV and their prodrugs are the first choice for these viral infections.

However, the long-term treatment of immunocompromised patients with these drugs results in the development of resistant viruses which cause sometime serious life-threatening infections in immunocompromised hosts. The majority of clinically isolated resistant strains have the mutation(s) in TK gene in HSV and VZV or UL 97 gene in HCMV, while some has the mutations in both viral phosphotransferase gene and viral DNA polymerase gene.

BVDU, a pyridine-containing nucleoside analogue, is a potent inhibitor of herpesviruses and is especially effective against VZV (D e Clercq & Walker, 1984). BVDU is orally available and extremely successful in the treatment of herpes zoster (Wutzler et al., 1995). However, BVDU does not have worldwide approval for treatment of VZV infections; currently, it is approved only in Germany.

When virus resistant to the first line nucleoside analogues develops, either PFA or CDV are used as a second choice for treatment. PFA, a pyrophosphate analogue, directly inhibits the viral DNA polymerase (Crumpacker, 1992). CDV, a nucleoside phosphonate, becomes an active form by two cellular phosphorylation enzymes and inhibits viral DNA polymerase (Neyts & De Clercq, 1994; Cihlar & Chen, 1996). Both of these drugs show poor bioavailability. PFA is more widely distributed and is used for drug-resistant virus infections. Fomiviren is the first licensed antisense oligonucleotide to inhibit HCMV immediate-early 2 (IE2) gene transcription (Perry & Balfour, 1999). This drug is used only for the treatment of HCMV retinitis via direct intraocular inoculation (Leeds et al., 1997).

Treatment of immunocompromised patients with current antiviral drugs results in the development of drug-resistant virus. Because all of the current antivirals target the same active sites on viral kinase and viral DNA polymerase molecules, mutant virus resistant to one drug often show cross-resistance to other drugs. In addition, although ACV is not particularly toxic, all anti-HCMV drugs exhibit toxic side effects. These drawbacks of antivirals for herpesvirus infections can be overcome by new compounds that prevent viral replication by inhibiting either an entirely different enzyme function or one which is already targeted by virtue of a new compound binding site (Visalle & Zeijl, 2003).

**Inhibitors of viral DNA synthesis**

Non-nucleoside herpesvirus DNA polymerase inhibitors

Large libraries of compounds were screened (by automatic high-throughput in vitro assay) for inhibition of HCMV DNA polymerase identified naphthalene carboxamide, PNU-26370, as the lead compound. From PNU-26370,
4-hydroxyquinoline-3-carboxamides were chemically synthesized as a novel class of non-nucleoside, broad-spectrum inhibitors of herpesvirus DNA polymerases. Additional chemical modification of this class yielded the more potent 4-oxo-dihydroquinolines (4-oxo-DHQs) (Figure 2), as represented by PNU-182171 and PNU-183792 (Brideau et al., 2002; Knechtel et al., 2002; Wathen, 2002). PNU-182171 and PNU-183792 inhibited not only the HCMV DNA polymerase, but also the HSV-1, HSV-2 and VZV DNA polymerases, and PNU-183792 was also shown to inhibit the HHV-8 DNA polymerase. In contrast, PNU-183792 did not inhibit the HHV-6 DNA polymerase. These compounds did not inhibit the polymerase activity of cellular DNA polymerases α or δ; nor do they inhibit the mitochondrial DNA polymerase γ. In antiviral cell culture assays, PNU-182171 and PNU-183792 inhibited replication of HSV-1, HSV-2, VZV and HCMV; PNU-183792 was also shown to inhibit the HHV-8 replication. However, in agreement with the in vitro polymerase assay, PNU-183792 did not inhibit the replication of HHV-6.

In order to investigate the mode of action of the 4-oxo-DHQs, HSV-resistant viruses were selected in the presence of 20 µM PNU-182171 (Thomsen et al., 2003). The sequencing of the mutants' DNA polymerase genes revealed that they carried a single point mutation, resulting in a V823A amino acid (or the equivalent amino acid in HSV-2) change, located within conserved domain III of the herpesvirus DNA polymerase gene. HCMV-resistant virus was also found to have amino acid changes at V823A and V824L within conserved domain III. V823 is conserved in the DNA polymerase of six of the eight human herpesviruses (HSV-1, HSV-2, VZV, HCMV, EBV and HHV-8); polymerase of the other two, HHV-6 and HHV-7, contained an alanine at codon 823. In HHV-6 polymerase, the change of amino acid from alanine to valine at codon 823 altered polymerase activity, resulting in inhibition of the enzyme by 4-oxo-DHQs. In addition, the 4-oxo-DHQ-resistant HSV-1, HSV-2 and HCMV mutants did not have altered susceptibility to current nucleoside analogues; in fact, some mutants were hypersensitive to several of the drugs (Thomsen et al., 2003). 4-oxo-DHQs' broad spectrum of antiviral activity against herpesviruses in immunocompromised patients (Wathen, 2002).

**Helicase/primase complex inhibitors**

The helicase/primase complex is known to be an essential component of the DNA replication of herpesviruses (Crumpacker & Shaffer, 2002). The HSV helicase/primase complex is composed of three viral proteins (the products of UL5, UL8 and UL52 genes) and contains intrinsic DNA helicase, RNA polymerase (primase) and ssDNA-stimulated ATPase activities (C. Crute & Lehman, 1991; Zhu & Weller, 1992). The helicase/primase complex unwinds double-stranded viral DNA and generates primers for lagging strand synthesis by the viral DNA polymerase (Figure 1). The two different thiazole urea and thiazolylphenyl...
**Table 1. Diseases caused by human herpesviruses**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Immunocompetent host</th>
<th>Immunocompromised host</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary</td>
<td>Recurrent</td>
<td>Disseminated infection in adults and neonates</td>
</tr>
<tr>
<td>HSV-1</td>
<td>Gingivostomatitis, Pharyngitis, Encephalitis, Genital herpes</td>
<td>Herpes labialis, Herpes keratitis</td>
<td>Disseminated infection in adults and neonates</td>
</tr>
<tr>
<td>HSV-2</td>
<td>Genital herpes, Neonatal herpes</td>
<td>Genital herpes</td>
<td>Disseminated infection in neonates</td>
</tr>
<tr>
<td>VZV</td>
<td>Varicella</td>
<td>Herpes zoster</td>
<td>Disseminated infection, Encephalitis, Pneumonitis</td>
</tr>
<tr>
<td>HCMV</td>
<td>CMV mononucleosis, Congenital cytomegalic inclusion disease</td>
<td>Varicella</td>
<td>Disseminated infection, Pneumonitis Hepatitis, Encephalitis, Retinitis, Digestive ulcer, etc.</td>
</tr>
<tr>
<td>EBV</td>
<td>Infectious mononucleosis</td>
<td>Varicella</td>
<td>Disseminated infection, Pneumonitis Hepatitis, Encephalitis, Retinitis, Digestive ulcer, etc.</td>
</tr>
<tr>
<td>HHV-6, -7</td>
<td>Roseola infantum</td>
<td>?</td>
<td>None</td>
</tr>
<tr>
<td>HHV-8</td>
<td>?</td>
<td>Kaposi’s sarcoma, Primary effusion lymphoma, Multicentric Castleman’s disease</td>
<td>None</td>
</tr>
</tbody>
</table>

ACV, acyclovir; CDV, cidofovir; CMV, cytomegalovirus; EBV, Epstein-Barr virus; FAM, famciclovir; GCV, ganciclovir; HCMV, human cytomegalovirus; HHV, human herpes virus; HSV, herpes simplex virus; PCV, penciclovir; PFA, foscarnet; VAL, valacyclovir; VGV, valganciclovir; VZV, varicella zoster virus.

**Figure 3.** The inhibitors of helicase and primase

![Figure 3](image-url)
derivatives target and inhibit H SV helicase/primase complex (Figure 3) (Crute et al., 2002; Kleymann et al., 2002; Crumpacker & Schaffer, 2002). The thiazole urea derivative, BAY-57-1293, inhibited ssDNA-stimulated ATPase activity and the thiazolylphenyl derivative, BILS 179BS, inhibited the activities of viral helicase, primase and ssDNA-stimulated ATPase. The enhancement of affinity between enzyme and DNA by BILS 179 BS resulted in preventing the propagation of H SV helicase/primase catalytic cycles (Crute et al., 2002). Both of these compounds inhibited the in vitro replication of H SV-1 and H SV-2 more effectively than ACV, and were also effective against ACV-resistant H SV and PAA-resistant H SV-1 (Kleymann et al., 2002). In contrast, these compounds showed almost no activity against VZV or H CMV replication. Ten drug-resistant H SV mutants were selected in the presence of 0.5–2.0 µM BAY 57-1293. The frequency of the appearance of mutants (0.5–4.5 ×10⁻¹⁵) is at least one order of magnitude lower compared with ACV. The mutations in isolated mutants in vitro resistant to these compounds map to UL5 and UL52 genes, indicating that both compounds target helicase/primase complex. The mutations in the UL5 gene of H SV-1 were mainly found between codon 349–359 (the α-helix stretch H E F G N L M K V L E), which is adjacent to the conserved motif IV of the six protein domains required for helicase activity (Kleymann et al., 2002).

These two compounds exhibit low toxicity and a high bioavailability (>60%) in animal models. Both BILS 179 BS and BAY 57-1293 were active orally and showed impressive effects on the healing of H SV-1 and H SV-2 in cutaneously infected mice and H SV-2 in vaginally infected guinea pigs (Kleymann et al., 2002; Crute et al., 2002; Betz et al., 2002). Topical treatment of zosteriform H SV infection with BAY 57-1293 was also effective. In these animal model experiments, both derivatives were superior to ACV and valaciclovir: they reduced time to healing, prevented rebound of disease after cessation of treatment and reduced frequency and severity of recurrent disease. Therefore, the clinical application of these derivatives will be expected to significantly improve the treatment of H SV disease in humans, including those resistant to current medications.

Another compound with a different chemical composition, T-0902611, is a specific inhibitor for H CMV. T-0902611 covalently modifies the H CMV primase component of the helicase/primase complex (Chen et al., 41st Interscience Conference on Antimicrobial Agents & Chemotherapy (ICAC), 2001, A bstr. F-1672; Powers et al., 41st IC AAC, 2001, A bstr. F-1673), T-0902611 is reported to have 30-fold better activity than GCV in vitro. Phase I studies show that the drug was well-tolerated with no observable toxicity to bone marrow. However, a precise evaluation of this drug has not yet been published.

Inhibitors of DNA encapsidation

In the replication of herpesviruses, viral DNA polymerase produces large, complex head-to-tail concatamers (Zhang et al., 1994; Severini et al., 1996) which must be cleaved into genome-length pieces before insertion into preformed capsids (Figure 4). Seven H SV-1 genes have been found to be involved in concatenate cleavage and packaging (Visalli & Zeijl, 2003). They are UL6, UL15, UL17, UL25, UL28, UL32 and UL33. The homologues of these genes exist in other herpesviruses; in the case of H CMV, for example, they are UL104, UL89, UL93, UL77, UL56, UL52 and UL51, respectively (Chee et al., 1985). H CMV UL56 and UL89 products are thought to make up the heterodimeric H CMV terminase complex (Schefczik et al., 2002; Giesen et al., 2000). The H CMV UL56 and UL56 complex has DNA binding activity and specifically recognizes packaging (pac) sequences located near the ends of herpesvirus genomes (Bonger et al., 1998). In addition, the UL89/UL56 complex possesses nucleolytic activity and ATPase activity (Figure 4). Another key protein in encapsidation is H SV-1 UL6 and the equivalent gene products of other herpesviruses (Figure 4). The UL6 gene product forms the portal protein through which the DNA can enter the procapsid (Newcomb & Brown, 1994, 2002; Newcomb et al., 2001a,b).

Inhibitors of terminase complex

The first compounds targeting H CMV terminase complex were benzimidazole ribonucleoside derivatives, BDCRB and TCRB. These compounds were potent and selective inhibitors of H CMV replication but not murine CMV (Townsend et al., 1995). Mutants resistant to TCRB and BDCRB had the mutations in H CMV UL56 and UL51 genes (Underwood et al., 1998; Kroisky et al., 1998). It was also revealed that BDCRB inhibits the nucleasie activity of UL89 gene product and ATPase activity of UL56 gene product (Schefczik et al., 2002; Scholz et al., 2003). Although these compounds showed good oral bioavailability, half-life in the plasma is relatively short (Good et al., 1994). Therefore, many additional analogues were synthesized, including 1263W94 (maribavir) and 275175X (175X). Although 175X is an analogue of BDCRB in which D-ribose is in the pyranosyl form, maribavir is an L-ribofuranosyl nucleoside (W illiams et al., 2003). 175X exhibits greater bioavailability and reduced serum protein-binding. This compound acts as an inhibitor of terminase complex, similar to BDCRB (Figure 4). Maribavir has a completely different function, as described later.

Another class of compound, phenylenediamine-sulphonamide (BAY 38-4766), was reported to inhibit the cleavage of concatenated H CMV DNA in cell culture (Buerger et al., 2001). The resistant mutations have been mapped in H CMV UL89 and UL56 genes (Buerger et al., 2001).
Figure 4. The inhibitors of terminase complex

GW 275175X

BAY38-4766

Figure 5. The inhibitors of portal protein

WAY-150138

Comp 1
Antiherpes activity of synthetic pregnanes

However, BAY 38-4766 has a different molecular mode of action from benzimidazole ribonucleosides; BAY 38-4766 resistant mutants did not show cross-resistance to benzimidazole ribonucleoside derivatives (Evers et al., 2002). In addition, BAY 38-4766 inhibited not only the replication of HCMV, but also animal CMVs such as murine CMV, rat CMV and rhesus CMV (Buerger et al., 2001; Reefshlaeger et al., 2001; Weber et al., 2001). Phase I clinical trails revealed that BAY 38-4766 was well-tolerated and achieved plasma concentrations in excess of HCMV IC50 with a single dose of 500 mg or greater (Reefshlaeger et al., 2001; Weber et al., 2001).

Inhibitors of portal protein

Two thiourea derivatives, WAY-150138 and Comp 1, were reported to inhibit HSV-1 and VSV, respectively (Figure 5). WAY-150138 specifically inhibited HSV-1, but not other herpesviruses; Comp 1 specifically inhibited VZV, but not other human herpesvirus or simian varicella virus (SVV) (van Zeijl et al., 2000; Visalli et al., 2003). The mutations resistant to WAY-150138 and Comp 1 have been mapped to HSV UL6 gene and VZV ORF54 gene (the UL6 equivalent of HSV), respectively (van Zeijl et al., 2000; Visalli et al., 2003). Although there was minimal difference between the two derivatives, reciprocal activity was not observed.

Other inhibitors

5-Chloro-1,3-dihydroxyacridone, a cellular topoisomerase II inhibitor, was reported to inhibit the replication of HSV (Figure 6). This compound inhibited DNA maturation and also reduced capsid production (Akanitapichat & Bastow, 2002). Because drug resistant mutants have not yet been isolated, the precise target of this compound remains undefined at present.

Recently, bicyclic furopyrimidine nucleosides bearing an aryl side chain (BCNAs) have been proved to be highly potent and selective inhibitors for VZV (McGugan et al., 2000). Some of these compounds were 10000-fold more effective than ACV.

Figure 6. The structure of 5-chloro-1,3-dihydroxy-acridone

Inhibitor of HCMV UL97 protein kinase

As mentioned above, maribavir is an unnatural L-ribofuranosyl nucleoside (Figure 7). Maribavir showed significant antiviral potency in vitro against both laboratory strains and clinical isolates of HCMV, including those resistant to GCV, PFA and BDCRB (McSharry et al., 2001; Williams et al., 2003). The mutation in maribavir-resistant mutants has been mapped to the HCMV UL97 protein kinase gene (Biron et al., 2002; Baek et al., 2002). Indeed, it has been shown that maribavir targets UL97 protein kinase and inhibits the activity of wild-type UL97 protein kinase (Biron et al., 2002). However, it is still controversial which stage of the replication cycle is inhibited by maribavir because the precise function of UL97 protein kinase in the replication cycle has not yet been demonstrated. One group reported that maribavir inhibited viral DNA replication without the inhibition of viral DNA polymerase (Biron et al., 2002), while another reported that maribavir blocks HCMV replication at the stage of nuclear egress, when DNA-containing capsids are transferred from nucleus to cytoplasm (Krosky et al., 2003). A third group reported that UL97 null mutants mainly block at the stage of encapsidation of viral DNA without effects on viral DNA cleavage (Wolf et al., 2001).

Maribavir was safely administered as single oral dose of 50 to 1600 mg to healthy and HIV-infected adults and pharmacokinetics (PK) were dose proportional over the dose range tested. Phase I trial revealed that maribavir was rapidly absorbed after oral dosing and demonstrated linear PK with steady-state plasma maribavir profiles. Maribavir showed in vivo anti-HCMV activity in semen in HIV-infected adults, with mean reduction in semen HCMV titres of 2.9–3.7 log10 (Lalezari et al., 2002). Maribavir was generally well-tolerated and most frequently reported side effect was taste disturbance. Although the precise stage at which maribavir is effective is still controversial, clinical application of maribavir will be expected in the near future.

Several protein kinase inhibitors (PKIs) were analysed and indolocarbazoles, K252a, K252c and G6976, proved...
to be highly effective inhibitors of GCV-sensitive and resistant HCMVs (Zimmerman et al., 2000). These compounds were fully effective when added up to 24 h post-infection. These indolocarbazoles strongly inhibited both autophosphorylation of UL97 protein and UL97 protein kinase-dependent phosphorylation of GCV.

Cellular proteins as antiviral targets

To ensure specificity and avoid toxicity, the antivirals currently available target viral proteins. The drawbacks of such drugs is that they only exhibit activity against a few closely related viruses and contribute to the development of resistant viruses. In contrast, the antiviral drugs targeting cellular proteins essential for viral replication would not be constrained by these limitations (Coen & Schaffer, 2003). However, the inhibitors of cellular proteins may show significant side effects. Although antivirals targeting cellular protein are not yet available, some inhibitors of cellular proteins inhibit viral replication.

A pharmacological cyclin-dependent kinase (cdk) inhibitor, roscovitine, inhibited H SV-1, H SV-2 and H IV-1, but not vaccinia virus or lymphocytic choriomeningitis virus (LCMV); inhibited replication of strains of H SV-1 and H IV-1 resistant to conventional antiviral drugs; and binds to the same subset of proteins in mock- and H SV-infected cells (Schang et al., 2002). These lines of evidence indicate that roscovitine inhibits virus replication by targeting cellular proteins. However, roscovitine is rather less effective than indolocarbazoles, protein kinase inhibitors (PKIs) (Zimmerman et al., 2000).

A novel cellular target is cyclooxygenase-2 (COX-2) which is one of the cellular enzymes induced after HCMV infection (Zhu et al., 2000). Prostaglandin E2, a product of COX-2 activity, is also produced more than 50-fold after HCMV infection. Non-cytotoxic COX-2 inhibitors inhibited the induction of COX-2, prostaglandin E2 and the replication of HCMV by 100-fold. COX-2 inhibitors block accumulation of HCMV immediate early 2 (IE2) but not IE1, mRNA or viral DNA replication.

Conclusions

As the number of immunocompromised hosts, such as cancer, organ transplant and AIDS patients, has increased, the need for controlling herpesvirus infections has become routine everywhere. Since idoxuridine was first introduced to treat herpes keratitis, effective antivirals have been developed and used for the treatment of herpesvirus infections. Because nearly all of these antivirals target viral DNA polymerase, long-term therapy leads to the appearance of drug-resistant viruses. In the past several years, however, new antivirals which target different viral proteins have been developed to overcome cross-resistance. Although these new compounds are still at the pre-clinical phase, some compounds are expected to reach the clinical stage in the near future.

The current range of antivirals and all the new compounds target the viral molecules essential for viral replication; how to eliminate latent virus still remains to be elucidated. In order to address this issue, it is essential that the viral and cellular molecular mechanisms involved in latency are elucidated.

References


cytomegalovirus DNA maturation by a benzimidazole ribonucleoside is mediated through the UL 89 gene product. Journal of Virology 72:717–725.


