Simian homologues of human herpesvirus 8

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γ -Herpesviruses can be found in most primates including Old World and New World monkeys. The γ -herpesvirinae are grouped into two classes: lymphocryptoviruses (γ_1) and rhadinoviruses (γ_2). The lymphocryptoviruses include Epstein–Barr virus, lymphocryptovirus of rhesus monkeys, and *Herpesvirus papio* of baboons. Rhadinoviruses that infect New World monkeys include *Herpesvirus saimiri*, whose natural host is the squirrel monkey, and *Herpesvirus ateles*, which infects spider monkeys. Rhadinoviruses that infect hominoids and Old World monkeys include Kaposi's sarcoma-associated herpesvirus, also known as HHV-8, and rhesus monkey rhadinovirus.

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1. INTRODUCTION

Primates can be classified into two groups: Prosimians and Anthropoids. Prosimians are the earliest and most primitive of primates (figure 1). Anthropoids are classified into two groups: platyrrhines (flat nosed) and catarrhines (downward-pointing nose). The platyrrhines are New World monkeys found exclusively in Central and South America, and Mexico. This group includes tamarins, marmosets, squirrel and spider monkeys (figure 2). The catarrhines consist of Old World monkeys, great apes and humans (figure 2). Old World monkeys are found in both Africa and Asia. The rhesus monkey (*Macaca mulatta*) is an example of an Old World primate found in Asia, while green monkeys and baboons are Old World primates found exclusively in Africa. The apes are divided into three groups; the Pongidae (orang-utans) and Hylabataidae (gibbons) live in Asia and the Panidae, including gorillas and chimpanzees, live in Africa. It is generally thought that the platyrrhines evolved after the separation of the continents or possibly crossed the ocean by rafting at a period in time when sea levels were lower.

The discovery of human γ -herpesvirus 8 (HHV-8) shattered the prevailing view regarding an evolutionary break in the phylogeny of γ -herpesviruses. *Herpesvirus saimiri* (HVS)-like viruses were found in New World primates and more primitive species, while viruses similar to Epstein–Barr virus (EBV) were found in Old World primates, great apes and humans. The general thinking at the time was that the Old World–New World split resulted in dramatic changes in γ -herpesvirus evolution, including the acquisition of Epstein–Barr nuclear antigen and EBV-encoded small RNA (EBER) genes and a tropism for B cells. However, it is now clear that γ_2 -herpesviruses (rhadinoviruses) can be found all through the mammalian class (figure 2). This new vision has been confirmed by the demonstration of natural infection of

macaque monkeys (Old World primates) with HHV-8-like γ_2 -herpesviruses.

Rhadinoviruses that infect New World monkeys include HVS, whose natural host is the squirrel monkey, and *Herpesvirus ateles* (HVA), which infects spider monkeys (figure 2) (Meléndez *et al.* 1969, 1972). Among Old World primates, rhesus monkey rhadinovirus (RRV) and closely related viruses from other macaque species, called RV2mac in this review (table 1), are γ_2 -herpesviruses of the macaque genus (Desrosiers *et al.* 1997). The similarity between the genomes of RV2mac and HHV-8 is high and almost all of the open reading frames (ORFs) in HHV-8 have at least one homologue in RV2mac (Alexander *et al.* 2000; Searles *et al.* 1999). RV2mac replicates lytically in cultured cells and multiple isolates have been obtained independently by different laboratories (Desrosiers *et al.* 1997; Searles *et al.* 1999). Rhadinoviruses closely related to the original isolates from rhesus monkeys (RRV; RV2mac) have now been cultured from other macaque species, specifically *Macaca nemestrina* and *Macaca fascicularis* (Auerbach *et al.* 2000; Mansfield *et al.* 1999). We call these RV2mac isolates RV2mmu, RV2mfa, and RV2mne in this review.

Short stretches of related but phylogenetically distinct sequences have also been amplified from *Macaca mulatta* and *Macaca nemestrina* (Bosch *et al.* 1999; Rose *et al.* 1997; Schultz *et al.* 2000; Strand *et al.* 2000). The putative viruses represented by these species, called RV1mmu and RV1mne in this review, have not been cultured and more detailed information on genomic organization and sequence relatedness is keenly awaited. Short stretches of related sequence have also been amplified from African green monkeys (*Chlorocebus aethiops*). The putative viruses represented by these sequences fall into two phylogenetic groupings called RV1agm and RV2agm, neither of which has yet been successfully cultured (Greensill *et al.* 2000). Short stretches of rhadinovirus sequences have also been amplified from chimpanzees and gorillas (Lacoste *et al.* 2000; T. Schulz, personal communication). Again, the putative viruses have not been cultured and the related

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Figure 1. Primate classification. Primates are classified into two groups, prosimians and anthropoids.

rhadinovirus sequences from chimpanzees again fall into two phylogenetic groupings.

2. PHYLOGENETIC ANALYSIS

A simplified nomenclature system that will be used for this review is shown in table 1. Rhadinoviruses from macaque monkeys that have been cultured and that are similar to the initial isolates 2695 and 17577 will be referred to as RV2mac. Individual isolates or strains are designated by species and number, e.g. RV2mmu2695, RV2mmu17577 and RV2mfa2797, where mmu and mfa are *Macaca mulatta* and *Macaca fascicularis*, respectively. Similarly, the putative viruses RFHvMm and RFHvMn are called RVlmmu and RVlmne here.

Sequences from the DNA polymerase genes from both isolated and putative primate γ_2 -herpesviruses were used to construct a phylogenetic tree (figure 3). Published sequences of the polymerase chain reaction (PCR) products of the DNA polymerase genes from RVlagm, RV2agm, RVlmmu, RVlmne and RV2mn were used (Bosch *et al.* 1999; Rose *et al.* 1997; Schultz *et al.* 2000; Strand *et al.* 2000). For RVlagm and RV2agm, Greensill *et al.* (2000) PCR-amplified 1802 bp and 454 bp of the DNA sequence. For RVlmmu and RVlmne, 3540 bp and 3554 bp of DNA sequences were amplified (Strand *et al.* 2000). These latter sequences include the C-terminus of the glycoprotein B (gB) gene, an intact DNA polymerase gene and the N-terminus of the HVS ORF 10 homologue in the same linear order found in HHV-8. The PCR-amplified sequences represent only portions of the entire genomic sequences of these putative viruses. The phylogenetic analyses suggest the presence of at least two distinct lineages of HHV-8-like rhadinoviruses in primates. One lineage contains HHV-8, RVlmmu, RVlmne and RVlagm, and the other contains RV2mmu, RV2mne and RV2agm. The latter branch is closer than the former to HVA and HVS. Surprisingly, a given lineage in green monkeys is more closely related to the corresponding lineage in macaques than to the other lineage from green monkeys (figure 3). This observation suggests an ancient origin for the two lineages or that one or more of the viruses represents cross-species transmission. It also raises

the question of whether a second major phylogenetic grouping of rhadinoviruses may be found in humans. Current evidence thus suggests that there are two distinct lineages of primate rhadinoviruses, both of which are similar to HHV-8.

3. PREVALENCE OF RV1 AND RV2

More than 90% of adult macaques at the New England Regional Primate Research Center (NERPRC) are sero-positive for RV2mac (Desrosiers *et al.* 1997; Mansfield *et al.* 1999). A similar frequency of infected macaques was also found at the Oregon Regional Primate Research Center (ORPRC) (Wong *et al.* 1999). This strongly suggests that RV2mac is a natural infectious agent of macaques. RV2mac isolated from one species can readily infect macaques of another species upon experimental inoculation (Mansfield *et al.* 1999). NERPRC groups macaques according to species, including infants that are housed with their natural mothers. Transmission is thought to occur from infected adults to juveniles through close contact. Newborn macaques can be raised free of RV2mac by hand-rearing (Mansfield *et al.* 1999). Although gB sequences of RV2mac isolates from three different species were all closely related, they did cluster according to species of origin (Auerbach *et al.* 2000). They did not group according to the facility where the monkeys were housed (Auerbach *et al.* 2000). A limited study of R1 sequences of RV2mac from three different species did not reveal a clustering according to species of origin (Damania *et al.* 1999). Sufficient information is not available for RVlmac to gauge prevalence or even whether macaques are indeed a natural host.

For RVlmac, 9 out of 40 *Macaca nemestrina* monkeys with retroperitoneal fibromatosis (RF) were positive for RVlmne by PCR, while two out of two *Macaca mulatta* monkeys with RF were positive for RVlmmu. Two out of two unaffected *Macaca nemestrina* monkeys were negative for RVlmne by PCR (Bosch *et al.* 1999; Rose *et al.* 1997). For African green monkeys, 6 out of 68 monkeys showed the presence of RVlagm sequences in peripheral blood by PCR while 21 out of 68 monkeys were positive for RV2agm (Greensill *et al.* 2000).

Table 1. *Primate rhadinovirus nomenclature*

(Abbreviations: agm, African green monkeys; caa, *Chlorocebus aethiops aethiops*; cap, *Chlorocebus aethiops pygerythrus*; cas, *Chlorocebus aethiops sabaues*; mac, macaques; mfa, *Macaca fascicularis*; mmu, *Macaca mulatta*; mne, *Macaca nemestrina*; pt, *Pan troglodytes*.)

general name	specific name	examples of designations	original name	reference
RV2mac	RV2mmu	RV2mmu2695	RRV26-95	Desrosiers <i>et al.</i> (1997)
		RV2mmu17577	RRV17577	Searles <i>et al.</i> (1999)
	RV2mne	RV2mne442N	Mne442N	Strand <i>et al.</i> (2000)
	RV2mfa	RV2mfa4797	Mf27-97	Auerbach <i>et al.</i> (2000)
RV1mac	RV1mmu	—	RVHvMm	Rose <i>et al.</i> (1997)
	RV1mne	—	RBHvMn	Rose <i>et al.</i> (1997)
RV1agm	RV1caa	—	—	Greensill <i>et al.</i> (2000)
	RV1cap	—	—	Greensill <i>et al.</i> (2000)
	Rv1cas	—	—	Greensill <i>et al.</i> (2000)
RV2agm	RV2caa	—	—	Greensill <i>et al.</i> (2000)
	RV2cap	—	—	Greensill <i>et al.</i> (2000)
	RV2cas	—	—	Greensill <i>et al.</i> (2000)
RV1pan	RV1pt	—	—	LaCoste <i>et al.</i> (2000)
RV2pan	RV2pt	—	—	LaCoste <i>et al.</i> (2000)

4. NON-HUMAN PRIMATE MODELS OF HHV-8 INFECTION AND DISEASE

Progress in defining the HHV-8 agent and the functional activities of the HHV-8 gene products has been phenomenal. However, two features of the HHV-8 system are likely to limit future progress. First is the absence of a traditional, permissive, lytic system for replication of HHV-8. Several EBV-negative B-cell lines derived from body-cavity-based lymphomas harbour HHV-8 sequences in such a way that they can be induced upon chemical stimulation to produce HHV-8. However, the amounts produced are small and a complete viral life cycle starting with infection is not present. Systems for serial propagation of HHV-8 have proven elusive to identify. Limited replication and serial transmission have been achieved in 293 cells but levels were so low that they could only be detected by PCR (Foreman *et al.* 1997). The lack of a traditional permissive system limits the ability to study the temporal order of events of the full virus life cycle and limits the ability to derive a genetic system for the construction of gene knock-out, mutant, and recombinant strains of virus. The simple question of 'is a gene required for virus replication?' becomes difficult to address in the absence of a manageable system for doing genetics. The second difficulty is the absence of an animal model, even a closely matched analogue model. The situation is analogous to that faced by AIDS researchers a number of years ago. Simian immunodeficiency virus (SIV) infection of rhesus monkeys was developed as a closely matched analogue model. Use of this analogue model has (i) provided important information on the relative importance and functional contribution of auxiliary genes; (ii) facilitated our understanding of immunopathogenic mechanisms through timed samplings and samplings of compartments in experimentally infected monkeys that would not be possible in humans; and (iii) been used extensively to guide vaccine and drug development efforts.

Wong *et al.* (1999) at the ORPRC experimentally inoculated rhesus macaques with RV2mmu17577 with and without SIVmac239 co-infection to determine whether RV2mmu17577 played a role in the development

of lymphoproliferative disease. In contrast to two control animals inoculated with SIVmac239 or RV2mac alone, two out of two animals co-infected with SIVmac239 and RV2mmu17577 developed hyperplastic lymphoproliferative disease resembling the multicentric plasma cell variant of Castleman's disease, characterized by persistent angiofollicular lymphadenopathy, hepatomegaly, splenomegaly and hypergammaglobulinaemia. Hypergammaglobulinaemia was associated with severe immune-mediated haemolytic anaemia in one macaque co-infected with RV2mmu17577 and SIV-infected macaque. Thus, experimental RV2mmu17577 infection of SIV-infected rhesus macaques was associated with the hyperplastic B-cell lymphoproliferative manifestations analogous to those seen in individuals infected with HHV-8 (Wong *et al.* 1999). Mansfield *et al.* (1999) at the NERPRC have also performed co-infections using RV2mmu2695 and SIVmac239. Experimental infection of macaques was associated with clinical lymphadenopathy characterized initially by paracortical hyperplasia and vascular hypertrophy or hyperplasia that subsequently was replaced by marked follicular hyperplasia. In the most severe cases, this follicular hyperplasia obliterated medullary sinuses and completely effaced the normal lymph node architecture. Similar changes have been found in HHV-8-infected, human immunodeficiency virus-negative patients with histological features of angioimmunoblastic lymphadenopathy and reactive lymphadenopathy. B-cell proliferation is a feature common to multicentric Castleman's disease and angioimmunoblastic lymphadenopathy (Mansfield *et al.* 1999). In addition, Mansfield *et al.* (1999) observed that three out of four monkeys co-infected with RV2mmu2695 and SIV developed an arteriopathy. This arteriopathy appeared fundamentally similar to the vascular endothelial lesion observed in patients with Kaposi's sarcoma (KS) and to the large vessel arteritis induced in mice infected with murine γ -herpesvirus 68 (MHV-68) (Mansfield *et al.* 1999). A causative role for RV2mac in arteriopathy and lymphoproliferative disease in the context of SIV-induced immune deficiency needs to be investigated more fully.

Figure 2. Classification of anthropoids. Anthropoids can be divided into two groups: Old World monkeys and New World monkeys. Examples of simian homologues of HHV-8 for each species are given in parentheses.

Although a reproducible system for the induction of KS or B-cell lymphoma in rhesus monkeys by RV2mac has not been achieved, at least as yet, a large number of critical questions can still be addressed using this system of experimental infection. These include the ability to define the relative importance of individual genes and their functional contribution to the establishment of primary infection, dissemination, persistence, tropism, pathological manifestations and immune-avoidance strategies.

5. THE RV2mac GENOME

Complete RV2mac genomes have been sequenced at two institutions, the ORPRC and the NERPRC. RV2mmu2695 from the NERPRC and RV2mmu17577 from the ORPRC (table 1) are very similar both in sequence and in genomic organization (Alexander *et al.* 2000; Searles *et al.* 1999). Only 4 out of the 84 ORFs exhibited less than 95% sequence identity at the amino-acid level.

The primary sequence of the long unique region of RV2mmu2695 consists of 130 733 bp that contain 84 ORFs (figure 4). The overall organization of the RV2mac genome was found to be very similar to that of human KS-associated herpesvirus (HHV-8) (Alexander *et al.* 2000). BLAST search analysis revealed that in almost all cases RV2mac coding sequences have greater degrees of similarity to corresponding HHV-8 sequences than to other herpesviruses. All of the ORFs present in HHV-8 have at least one homologue in RV2mac except K3 and K5 (bovine herpesvirus immediate early protein number 4 homologues), K7 (nut-1), and K12 (kaposin). RV2mac contains one MIP-1 and eight interferon regulatory factor (vIRF) homologues compared with three MIP-1 and four vIRF homologues in HHV-8. All homologues are

Figure 3. Phylogenetic analysis of the DNA polymerase genes of γ_2 -herpesviruses (adapted from Greensill *et al.* 2000). The distance tree was constructed by the neighbour-joining method using 151 amino-acid residues of DNA polymerase. Sequences were aligned using CLUSTALX and analysed with PROTDIST and NEIGHBOR programs in PHYLIP.

correspondingly located in HHV-8 and RRV with the exception of dihydrofolate reductase (DHFR). DHFR is correspondingly located near the left end of the genome in RRV2695 and HVS, but in HHV-8 the DHFR gene is displaced well downstream (figure 2). The location of the DHFR gene in HHV-8 is different from that in RV2mac

Table 2. Cellular homologues encoded by γ -herpesviruses

viral gene	EBV	HHV-8	RV2mac	HVS
transforming gene	LMP-1	K1	R1	STP
signal modulator	LMP-2A	K15	R15	Tip
cyclin	—	G1 v-cyclin	G1 v-cyclin	G1 v-cyclin
anti-apoptotic genes	vBcl-2	vBcl-2	vBcl-2	vBcl-2
		vFLIP	vFLIP	vFLIP
cytokines	vIL-10	vIL-6	vIL-6	vIL-17
chemokines	—	vMIPs	vMIPs	—

and HVS, suggesting that HHV-8 may have rearranged or reacquired the DHFR gene during the course of evolution from Old World primate to human rhadinoviruses. DHFR is also unusual in that the RV2mac DHFR more closely resembles HVS DHFR (74% similarity) than HHV-8 DHFR (55% similarity). Eighty-three out of the 84 ORFs in RV2mmu2695 contain sequences similar to those present in the independent RV2mmu17577 isolate. RV2mmu2695 and RV2mmu17577 sequences differ in that ORF 67.5 sequences contained in RV2mmu2695 were not found in RV2mmu17577. In addition, ORF 4 is significantly shorter in RV2mmu2695 than was reported for RV2mmu17577 (395 versus 645 amino acids) (Alexander *et al.* 2000; Searles *et al.* 1999). Only four of the corresponding ORFs between RV2mmu2695 and RV2mmu17577 exhibited less than 95% sequence identity: glycoproteins H and L, uracil DNA glycosidase, and a tegument protein (ORF 67). Both RV2mmu2695 and RV2mmu17577 have short, unique ORFs between 21444 and 21752 and 110 910–114 899 in a rightward direction, and 116 524 and 111 082 in a leftward direction that are not found in HHV-8. Analysis of the two genomes indicates that RV2mmu2695 and RV2mmu17577 are clearly independent isolates of the same virus species and both are closely related in structural organization and overall sequence to HHV-8 (Alexander *et al.* 2000; Searles *et al.* 1999).

The availability of detailed sequence information, the ability to grow RRV lytically in cell culture, and the ability to infect monkeys experimentally with RRV will facilitate the construction of mutant strains of virus for evaluating the contribution of individual genes to biological properties.

6. SIMILARITIES AMONG GENES ENCODED BY EBV, HHV-8, RRV AND HVS

HHV-8, RRV and HVS contain homologues of cellular genes, some of which have been shown to have transforming capabilities in culture. The γ_2 -herpesviruses often contain more cellular homologues than EBV. All four viruses contain discrete genes that are located in equivalent positions in the viral genomes that perform analogous functions despite any obvious similarity in primary sequence.

(a) Transforming genes

EBV, HHV-8, RV2mac and HVS contain several transforming genes at equivalent positions in the genome. A striking feature of these four γ -herpesviruses is that they contain a distinct ORF at the left end of their respective

genomes, each of which has characteristic transforming ability. These include the latent membrane protein 1 (LMP-1) of EBV, K1 of HHV-8, R1 of RV2mac, and saimiri transformation protein (STP) of HVS (table 2) (Biesinger *et al.* 1995; Desrosiers *et al.* 1985, 1986; Franken *et al.* 1996; Jung & Desrosiers 1991; Jung *et al.* 1991; Kasolo *et al.* 1998; Lagunoff & Ganem 1997; Lee *et al.* 1998a,b; Nicholas *et al.* 1997, 1998; Palefsky *et al.* 1996; Zong *et al.* 1999). This functional conservation exists in the complete absence of any sequence homology.

EBV LMP-1 has been shown to mimic an activated CD40 receptor and to interact with tumour necrosis factor (TNF) receptor-associated factors (TRAFs), with TNF-receptor-associated death domain (TRADD) and with receptor-interacting protein (Devergne *et al.* 1996, 1998; Eliopoulos *et al.* 1996, 1999; Izumi *et al.* 1997, 1999b; Sandberg *et al.* 1997). The interaction of LMP-1 with TRAFs and TRADD has been shown to be essential for the activation of the nuclear factor kappa B (NF- κ B) pathway and for EBV-induced immortalization of B lymphocytes (Izumi *et al.* 1999a; Kaye *et al.* 1999). HVS STP-C has also been shown to activate NF- κ B transcriptional activity by interacting with TRAFs 1, 2, and 3 (figure 2) (Lee *et al.* 1999). In addition, STP-C has been shown to associate with cellular RAS (Jung & Desrosiers 1995) and this interaction is critical for its transforming activity in cell culture. Finally, the cytoplasmic domains of both HHV-8 K1 and RV2 R1 can interact with the major B-cell kinase, syk, and transduce signals to induce nuclear factor of activated T cells' activation, calcium mobilization and tyrosine phosphorylation, events that are indicative of lymphocyte activation (Damania *et al.* 1999, 2000; Lagunoff *et al.* 1999; Lee *et al.* 1998a,b). These properties of K1 and R1 may contribute to their ability to transform rodent fibroblasts.

(b) Signal modulators

Genes for EBV LMP-2A, HHV-8 K15 and RV2mac R15 are located near the right end of their herpesviral genomes. The HVS Tip gene is located at the other end of the genome. The LMP-2A, K15 and Tip proteins are all capable of associating with the major B- or T-cell-receptor-associated kinases and altering their signalling activity (table 2). Cross-linking of the B-cell antigen receptor and T-cell antigen receptor triggers a signal transduction cascade that leads to the activation of B and T lymphocytes, respectively. The EBV LMP-2A, HHV-8 K15, HVS Tip and RV2mac R15 proteins can antagonize these signalling events, thus potentially preventing the reactivation of viral lytic infection from latently infected

Figure 4. Alignment of ORFs of HHV-8 and RV2mmu2695 (from Alexander *et al.* 2000). The different colours signify ORFs contained in HHV-8 and RV2mmu2695 that are conserved in the indicated herpesvirus subfamilies or subgroups. The square side of the symbol signifies the 5'-end and the pointed side of the symbol signifies the 3'-end of the depicted ORFs. The ORFs are not drawn to scale.

cells (Beaufils *et al.* 1993; Choi *et al.* 2000; Jung *et al.* 1995; Miller *et al.* 1994, 1995).

(c) Cellular homologues

A number of genes among the γ -herpesviruses show clear homology to cellular genes (table 2). These viral genes vary considerably in the degree to which they are related to their cellular counterparts. While EBV contains fewer homologues of cellular genes, HHV-8, RV2mac

and HVS contain many such genes that could potentially contribute to the deregulation of cellular growth. In many cases, rather than having independently captured the genes for its own genome, EBV appears to upregulate the expression of the cellular genes themselves.

(i) Viral cyclins

Cyclins are regulatory subunits of a specific class of cellular kinases and are known effectors of cellular

proliferation. While cyclins were originally identified as proteins of cellular origin, it now appears that many γ -herpesviruses contain within their genome a reading frame with sequence homology to cellular cyclins. The significance of the virally encoded cyclins (v-cyclins) in viral propagation and pathogenesis is as yet unclear. However, the fact that deregulation of cellular cyclin expression is a known event in tumour development suggests that v-cyclins could be part of mechanisms that ultimately lead to tumour formation. The v-cyclin encoded by MHV-68 induces cell-cycle progression and is an oncogene. Deletion of the v-cyclin gene from MHV-68 as well as truncation of the v-cyclin gene in recombinant MHV-68 yielded viruses that were defective for reactivation from latency (Hoge *et al.* 2000; Van Dyk *et al.* 2000).

While EBV upregulates the expression of cyclin D and cyclin E, HHV-8, RV2mac and HVS all encode their own G1 cyclin.

(ii) *Viral bcl-2 and viral FLIP*

Viral infection usually triggers a cellular response leading to apoptosis of the infected cell. The four γ -herpesviruses appear to have circumvented this host-defence mechanism by coming prepared with their own set of viral anti-apoptotic genes. EBV, HHV-8, HVS and RV2mac encode viral *bcl-2* genes, whereas only the rhadinoviruses contain viral FLICE inhibitory proteins (FLIPs).

(iii) *Cytokines*

All four γ -herpesviruses encode genes for cytokines that appear to enhance cellular proliferation and enable viral transformation of infected cells. EBV encodes a homologue of interleukin (IL)-10, HHV-8 and RV2mac encode a viral IL-6 and HVS encodes a viral IL-17. In addition HHV-8 and RV2mac also contain homologues of MIP-I, II and III chemokine genes.

7. CONCLUSIONS

DNA tumour viruses have provided the scientific community with important tools for the analysis of cellular pathways involving signal transduction, transcriptional regulation and cell growth transformation. Tumour viruses stimulate the proliferation of cells in which they establish long-term residence. Like other DNA tumour viruses, the γ -herpesviruses, EBV, HHV-8, RV2mac and HVS encode several viral genes that are capable of converting a normal cell to an abnormally proliferating one. This is achieved through a diverse array of viral genes, which target and modify different cellular proteins and pathways with the end result being beneficial to the survival and propagation of virus.

Two human γ -herpesviruses, EBV and HHV-8, have been identified to date. For both these viruses, corresponding simian homologues, rhesus EBV and RV2mac, have been isolated. Many of the genes encoded by these γ -herpesviruses show a high degree of similarity to their human counterparts. The simian viruses provide a means to model human infection with experimental protocols and settings that would not be possible in humans. While use of both RV2mac and rhesus EBC as animal models is

still in early developmental stages, they are likely to prove useful for studying the pathogenesis, prevention and treatment of EBV and HHV-8 infections.

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