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The family *Herpesviridae*: an update

Experiencing the universe is not the same
as systematizing it, no more than experiencing
love is the same as analyzing it.
Andre Malraux, *La Tentation de l'occident*

Introduction

More than 10 years have elapsed since the first report of the International Committee for the Taxonomy of Viruses (ICTV) Herpesvirus Study Group [187]. In that publication the Study Group designated *Herpesviridae* as the name of the herpesvirus family, erected three subfamilies, the *Alphaherpesvirinae, Betaherpesvirinae*, and *Gammaherpesvirinae*, and provided guidelines for the classification of herpesviruses into these subfamilies. Since that publication, the ICTV has approved the recommendation of previous Herpesvirus Study Groups to erect several genera. More important from the point of view of taxonomy and classification of herpesviruses, considerable amounts of new information regarding herpesviruses have accumulated in the past 10 years. Thus, (a) a large number of new herpesviruses has been discovered, (b) a few herpesviruses turned out to be contaminants, most likely derived from calf serum containing a bovine herpesvirus, (c) several herpesvirus genomes have been sequenced, (d) many highly conserved genes have been identified both within the family and in the individual subfamilies, and (e) we have a much better understanding at least of the problems facing the task of classifying herpesviruses. This paper updates the 1981 report.

Definition

Properties of herpesviruses: definition of the family Herpesviridae

Architecture of the virion

Inclusion of viruses into the family *Herpesviridae* is based on the architecture of the virion. A typical herpesvirion consists of (a) a core containing a linear double stranded DNA which, in some instances, forms a torus [84, 163], (b) an icosadeltahedral capsid approximately 100 to 110 nm in diameter containing 12 pentameric and 150 hexameric capsomeres, the latter with a hole running down the long axis [81, 231, 147]; (c) an amorphous, sometimes asymmetric material which surrounds the capsid and which was designated as the tegument [188]; and (d) a membrane designated as the envelope, in which viral glycoprotein spikes are embedded and project from its surface [4, 12, 75, 78, 99, 159, 160, 208, 209, 211].

The reported size of herpesvirions estimated from negatively stained preparations ranges from 120 to nearly 300 nm [188]. One possible explanation for this variability is the thickness of the tegument. The major source of variability, however, is the integrity of the envelope. Virions with intact envelopes are impermeable to negative stain and generally retain a

Table 1. Viruses comprising the family *Herpesviridae*

Designation	Common name (synonyms)	Sub-family	Genome			References
			G + C (mole %)	Group[a]	Size (kbp)	
Viruses of humans						
Human herpesvirus 1	herpes simplex virus 1	α	68.3	E	152	96, 148, 189, 199
Human herpesvirus 2	herpes simplex virus 2	α	69	E	152	189, 199
Human herpesvirus 3	varicella-zoster virus	α	46	D	125	57, 68, 189, 226
Human herpesvirus 4	Epstein-Barr virus	γ	60	C	172	6, 76, 120
Human herpesvirus 5	cytomegalovirus	β	57	E	229	45, 206, 207, 213
Human herpesvirus 6		β	42	A	162	132–134, 142, 196
Human herpesvirus 7		β				88
Viruses of nonhuman primates[b]						
Aotine herpesvirus 1	HV aotus type 1	β	55	E	220	1, 54, 69
Aotine herpesvirus 3	HV aotus type 3	β	56	D	219	69
Cercopithecine herpesvirus 1	B virus, HV simiae	α	75	E	160	192, 193
Cercopithecine herpesvirus 2	SA8	α	67	E	150	94
Cercopithecine herpesvirus 3	SA6	β	51			94, 140
Cercopithecine herpesvirus 4	SA15	β				140
Cercopithecine herpesvirus 5	African green monkey cytomegalovirus	β				17
Cercopithecine herpesvirus 6	Liverpool vervet monkey virus	α	52			49
Cercopithecine herpesvirus 7	patas monkey HV; MMV or PHV delta HV	α				146
Cercopithecine herpesvirus 8	rhesus monkey cytomegalovirus	β	52			5
Cercopithecine herpesvirus 9	Medical Lake macaque HV; simian varicella HV	α				18
Cercopithecine herpesvirus 10	rhesus leukocyte assoc. HV strain I					85
Cercopithecine herpesvirus 12	HV papio, baboon HV	γ	–	C	170	77, 103

Cercopithecine herpesvirus 13	herpesvirus cyclopis					110
Cercopithecine herpesvirus 14	African green monkey EBV-like virus	γ				18
Cercopithecine herpesvirus 15	rhesus EBV-like HV	γ				181
Ateline herpesvirus 1	spider monkey HV	α	72			94, 108
Ateline herpesvirus 2	HV ateles	γ	48	B	135	59, 79, 80, 154
Callitrichine herpesvirus 1	HV saguinus					153
Callitrichine herpesvirus 2	SSG, marmoset cytomegalovirus	β				168
Cebine herpesvirus 1	capuchin HV (AL-5)	β				131
Cebine herpesvirus 2	capuchin HV (AP-18)	β				193
Pongine herpesvirus 1	chimp. HV; pan HV	γ	–	C	170	102, 127
Pongine herpesvirus 2	orangutan HV	γ				182
Pongine herpesvirus 3	gorilla HV	γ				166
Saimiriine herpesvirus 1	marmoset HV; HV M, herpes T, HV tamarinus, HV platyrrhinae type	α	67	D	152	94, 105, 130
Saimiriine herpesvirus 2	squirrel monkey HV, HV saimiri	γ	46	B	155	22, 51, 223

Viruses of other mammals

Bovidae[c]

Bovine herpesvirus 1	infectious bovine rhinotracheitis HV	α	72	D	140	3, 90, 139, 145
Bovine herpesvirus 2	bovine mammillitis virus; Allerton virus, pseudo-lumpy skin disease HV	α	64	E	133	36, 37, 143, 214
Bovine herpesvirus 4	Movar HV	γ	50	B	145	9, 33, 220, 222
Bovine herpesvirus 5	bovine encephalitis HV	α	72	D	140	24, 73, 86
Ovine herpesvirus 1	sheep pulmonary adenomatosis associated HV			D	137	61, 62, 138
Ovine herpesvirus 2	sheep assoc. malignant catarrhal fever of cattle HV	γ		B		28
Caprine herpesvirus 1	goat HV	α				74, 195
Alcelaphine herpesvirus 1	wildebeest HV, malignant catarrhal fever HV of European cattle	γ	61	B	160	26, 27, 173, 174

Table 1 (continued)

Designation	Common name (synonyms)	Sub-family	Genome			References
			G + C (mole %)	Group[a]	Size (kbp)	
Alcelaphine herpesvirus 2	hartebeest HV	γ	–	B		185
Cervid herpesvirus 1	red deer HV	α	–	D		109, 165
Cervid herpesvirus 2	reindeer (*Rangifer tarandus*) HV	α	–	D		72
Canidae						
Canid herpesvirus 1	canine HV	α	32			215
Caviidae						
Caviid herpesvirus 1	guinea pig HV 1, Hsiung-Kaplow virus, GPHLV	γ	60			15, 81, 107, 162
Caviid herpesvirus 2	guinea pig cytomegalovirus	β	57			100, 156
Caviid herpesivurs 3	guinea pig HV 3, GPXV					16
Cricetidae						
Cricetid herpesvirus	hamster HV	β				Smith, 59
Elephanitidae						
Elephantid herpesvirus	elephant (loxodontal) HV					10, 175
Equidae						
Equid herpesvirus 1	equine HV 1; equine abortion HV	α	57	D	142	2, 180, 227
Equid herpesvirus 2	equine HV 2; equine cytomegalovirus	β	57	A	192	31, 32, 176
Equid herpesvirus 3	equine HV 3; equine coital exanthema virus	α	66	D	148	136, 216, 219
Equid herpesvirus 4	equine HV 4; equine rhinopneumonitis virus	α	56	D	148	53, 194, 217
Equid herpesvirus 5	equine HV 5	β			150	30
Equid herpesvirus 6	asinine HV 1	α				111
Equid herpesvirus 7	asinine HV 2	β				29
Equid herpesvirus 8	asinine HV 3	α				29

Erinaceidae						
Erinaceid herpesvirus 1[d]	European hedgehog HV					210
Felidae						
Felid herpesvirus 1	feline HV 1; feline rhinotracheitis HV	α	46	D	134	65, 175, 190
Leporidae						
Leporid herpesvirus 1	cottontail HV, HV sylvilagus	γ	33	B	145	94, 104, 149, 164
Leporid herpesvirus 2	HV cuniculi, virus III					164
Lorisidae						
Lorisine herpesvirus 1	kinkajou HV, herpes pottos					8
Macropodidae						
Macropodid herpesvirus 1	parma wallaby HV	α	53	D		114, 228
Macropodid herpesvirus 2	dorcopsis wallaby HV	α	50	E	135	114, 115
Marmodidae						
Marmodid herpesvirus 1	woodchuck HV HV marmota 1	γ	–	B	160	91, 197
Muridae						
Murid herpesvirus 1	mouse cytomegalovirus	β	59	F	235	70, 161, 205
Murid herpesvirus 2	rat cytomegalovirus	β	47			14, 150
Murid herpesvirus 3	mouse thymic HV					170, 191
Murid herpesvirus 4	mouse HV strain 68	γ		B	135	19, 71, 179
Murid herpesvirus 5	field mouse HV; *Microtus pennsylvanicus* HV					152
Murid herpesvirus 6	sand rat nuclear inclusion agent					155
Murid herpesvirus 7[e]	murine HV					19, 20
Phocidae						
Phocid herpesvirus 1	harbor seal HV					23, 169
Sciuridae						
Sciurid herpesvirus 1	European ground squirrel cytomegalovirus; American ground squirrel HV	β				7, 63
Sciurid herpesvirus 2						64

Table 1 (continued)

Designation	Common name (synonyms)	Sub-family	Genome			References
			G + C (mole %)	Group[a]	Size (kbp)	
Suidae						
Suid herpesvirus 1	pseudorabies virus, Aujeszky's disease	α	74	D	140	13, 97, 172
Suid herpesvirus 2	inclusion-body rhinitis virus, pig cytomegalovirus	β				128, 224
Tupaiidae						
Tupaiid herpesvirus 1	tree shrew HV		66	F	200	55, 125, 147, 157
Viruses of birds						
Anatidae						
Anatid herpesvirus 1	duck plague HV	α				11, 25
Accipitriae						
Accipitrid herpesvirus 1	bald eagle HV					66
Ciconiidae						
Ciconiid herpesvirus 1	black stork HV					117
Columbidae						
Columbid herpesvirus 1	pigeon HV-1		59			50, 129
Falconidae						
Falconid herpesvirus 1	falcon inclusion body disease virus					141
Gallidae						
Gallid herpesvirus 1	infectious laryngo-tracheitis virus	α	46	D	165	52, 129, 175, 144
Gallid herpesvirus 2	Marek's disease HV 1		47	E	180	44, 47, 83, 218
Gallid herpesvirus 3	Marek's disease HV 2					39, 202
Gruidae						
Gruid herpesvirus 1	crane HV					41
Meleagridae						
Meleagrid herpesvirus 1	turkey HV 1	γ	48	E	150	118, 129

Perdicid			
Perdicid herpesvirus 1	bobwhite quail HV		116
Phalacrocoracidae			
Phalacrocoracid herpesvirus 1	cormorant HV; Lake Victoria, cormorant HV	58	87, 129
Psittacidae			
Psittacid herpesvirus 1	parrott HV; recently rediscovered Pacheco's disease virus		203
Sphenicidae			
Sphenicid herpesvirus 1	black footed penguin HV		122
Stricidae			
Strigid herpesvirus 1	owl hepatosplenitis virus	61	40, 129, 198

Viruses of amphibia and reptiles

Boidae			
Boid herpesvirus 1[d]	boa herpesvirus		101
Chelonidae			
Chelonid herpesvirus 1[d] of green sea turtle	gray patch disease agent		98, 184
Chelonid herpesvirus 2[d]	Pacific pond turtle HV		82
Chelonid herpesvirus 3[d]	painted turtle HV, map turtle HV		51, 113
Chelonid herpesvirus 4[d]	*Geochelone chilensis* HV, *Geochelone carbonaria* HV, Argentine turtle HV		112
Elapidae			
Elapid herpesvirus	Indian cobra HV, banded krait, siamese cobra HV		137, 158
Iguanidae			
Iguanid herpesvirus 1	green iguana HV		48, 235
Lacertidae			
Lacertid herpesvirus 1	green lizard HV		183
Ranidae			
Ranid herpesvirus 1	Lucké frog HV	46	95, 135, 225
Ranid herpesvirus 2	frog HV 4	56	95, 178

Table 1 (continued)

Designation	Common name (synonyms)	Sub-family	Genome			References
			G + C (mole %)	Group[a]	Size (kbp)	
Viruses of bony fishes						
Cyprinidae						
Cyprinid herpesvirus	carp pox HV					201
Esocidae						
Esocid herpesvirus[d]	northern pike HV					234
Ictaluridae						
Ictalurid herpesvirus 1	Channel catfish HV	α	56	A	130	43, 46, 232
Percidae						
Percid herpesvirus 1	walleye epidermal hyperplasia virus					119
Pleuronectidae						
Pleuronectid herpesvirus	HV scophthalmus, turbot HV					35
Salmonidae						
Salmonid herpesvirus 1	HV salmonis					233
Salmonid herpesvirus 2	*Oncorhynchus masou* HV					121

[a] *A–F* Genome arrangements described in the text

[b] Aotine herpesvirus 2 [34, 67] and feline herpesvirus 2 [221] have been identified as BHV4. In accordance with the rules this number cannot be assigned to another herpesvirus

[c] Bovine herpesvirus 3 sometimes referred to as bovine herpesvirus 4 does not exist. These designations were applied to the virus acquired by cattle from the wildebeest in which it causes malignant catarrhal fever. The wildebeest virus is now called alcelaphine herpesvirus 1

[d] Indicates reports of herpesvirus-like particles in tissues but virus was not isolated in cell culture

[e] The inclusion of this virus in the list is provisional and subject to verification of lack of identity with other murine herpesviruses

quasi-spherical shape. Virions with damaged envelopes are permeable to negative stain and have a sunny-side-up egg appearance with an irregular shape and a diameter generally larger than that of an intact virion.

Herpesvirus genomes

The majority of herpesvirus DNAs extracted from virions are largely linear, double stranded molecules and those that have been studied in detail appear to have a 3′ single nucleotide extension [186, 189]. In the case of human herpesvirus 1 (HHV1, herpes simplex virus 1), and we assume this to be a general case, the DNA circularizes immediately upon release from capsids into the nuclei of infected cells [177]. The DNAs differ with respect to their size and base composition. The size of herpesvirus DNAs varies from approximately 124 to 235 kbp (Table 1). The size of the viral genomes is characteristic of each virus (species) and is not a reflection of polymorphism even though individual herpesvirus genomes vary slightly in size. The differences in the size of the genomes of independent isolates of the same virus species may be as high as 10 kbp and most frequently reflect the number of terminal and/or internal reiterated sequences. Spontaneous deletions also occur; they have been noted in both HHV1 and human herpesvirus 4 (HHV4, Epstein Barr virus or EBV) strains (e.g., EBV strain P3HR1 and in the isolate reported by Sixbey et al. [204], and HHV1 strain HFEM [123, 126]).

The base composition of herpesvirus DNAs varies from 32 to 75 G + C moles/cent (Table 1). Furthermore, herpesvirus DNAs vary with respect to the extent of homogeneity of base sequence distribution along the genome. The extent of inhomogeneity in the base composition varies from minimal (e.g., HSV) to very extensive (e.g., the DNAs of saimirine herpesvirus 2 and ateline herpesvirus 2, see [22]).

An intriguing feature of herpesvirus DNAs is their sequence arrangement. The sequence arrangement shown in Fig. 1 emphasizes the presence and location of reiterations of terminal sequences greater than 100 bp. According to this scheme, the herpesviruses can be divided into six groups designated by the letters A to F. In the genomes of viruses comprising group A and exemplified by the ictalurid herpesvirus 1 (channel catfish herpesvirus), equid herpesvirus 2, and the human herpesvirus 6 (HHV6), a large sequence from one terminus is directly repeated at the other terminus. In the group B genomes exemplified by saimirine herpesvirus 2, the terminal sequence is directly repeated numerous times at both termini; the number of reiterations at both termini may vary. In the group C genomes, exemplified by EBV, the number of direct terminal reiterations is smaller, but there may be other, unrelated, sequences greater than 100 bp that are directly repeated and which subdivide the unique (or quasi unique) sequences of genome into several well delineated stretches. In group D genomes exemplified by those of human herpesvirus 3 (HHV3, varicella zoster virus) and suid herpesvirus 1 (pseudorabies virus), the sequence at one terminus is repeated in an inverted orientation internally. In these genomes, the domain consisting of the stretch of unique sequences flanked by inverted repeats (short or S component) can invert relative to the remaining sequences (long or L component) such that the DNA extracted from virions or infected cells consists of two equimolar populations differing solely in the orientation of the S component relative to the fixed orientation of the L component. In group E viral genomes exemplified by those of HHV1, HHV2, and human herpesvirus 5 (HHV5, human cytomegalovirus), sequences from both termini are repeated in an inverted orientation and juxtaposed internally dividing the genomes into two components, L and S, each of which consists of unique sequences flanked by inverted repeats. In this instance, both

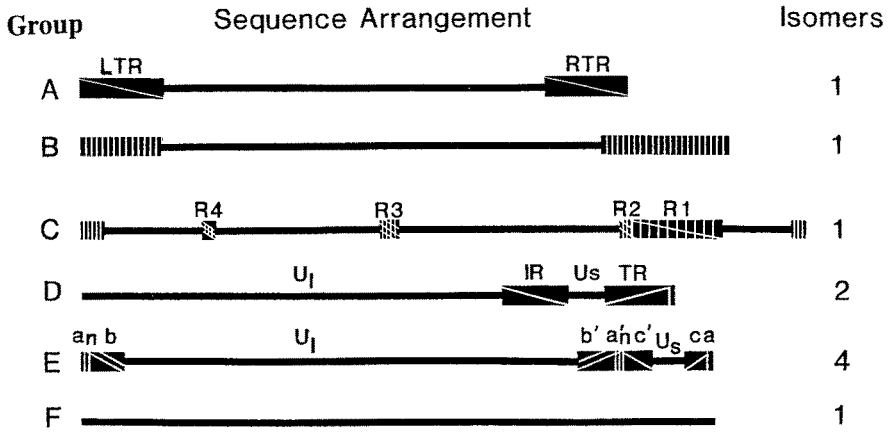

Fig. 1. A schematic diagram of the sequence arrangements in the 6 groups of genomes of the viruses comprising the family *Herpesviridae*. The genomes A, B, C, D, E, and F are exemplified by the ictalurid herpesvirus 1 (channel catfish herpesvirus), saimirine herpesvirus 2 (herpesvirus saimiri), human herpesvirus 4 (EBV), human herpesvirus 3 (VZV), human herpes virus 1 (HSV-1), and tupaiid herpesvirus 1 (tree shrew herpesvirus), respectively. In the schematic diagram the horizontal lines represent unique or quasi-unique regions. The reiterated domains are shown as rectangles and are designated as left and right terminal repeats (*LTR* and *RTR*) for group A, repeats R1 to R4 for internal repeats of group C, and internal and terminal (*IR* and *TR*) repeats of group D. The termini of group E (e.g., HSV) consist of two elements. One terminus contains n copies of sequence a next to a larger sequence designated as b. The other terminus has one directly repeated a sequence next to a sequence designated as c. The terminal $a_n b$ and ca sequences are inserted in an inverted orientation (denoted by primes) separating the unique sequences into a long (U_l) and short (U_s) domains. Terminal reiterations in the genomes of group F have not been described. In group B, the terminal sequences are reiterated numerous times at both termini. The number of reiterations at each terminus may vary. The components of the genomes in groups D and E invert. In group D, the short component inverts relative to the long. Although rarely the long component may also invert, most of the DNA forms two populations differing in the orientation of the short component. In the group E genomes, both the short and long components can invert and viral DNA consists of 4 equimolar isomers. From [186]

components can invert relative to each other and DNA extracted from virions or infected cells consists of four equimolar populations differing in the relative orientation of the two components. For the genomes comprising the F group exemplified by that of the tupaiid herpesvirus 1 (tupaia herpesvirus), the sequences at the two termini are not identical and are not repeated directly or in an inverted orientation.

Common properties of herpesviruses

The known herpesviruses have been shown to share four significant properties (reviewed in [186]).

(*i*) All herpesviruses specify enzymes and other factors involved in nucleic acid synthesis metabolism (e.g., DNA polymerase, helicase, primase, origin binding protein, etc.) as well as a variable number of enzymes involved in DNA metabolism (e.g., thymidine kinase, thymidylate synthetase, dUTPase, ribonucleotide reductase, etc.). Herpesviruses specify at least one protease and a variable number of protein kinases.

(*ii*) The synthesis of viral DNAs and assembly of capsids occur in the nucleus. In the case of some herpesviruses, it has been claimed that the virus may be de-enveloped and re-enveloped as it transits through the cytoplasm. Irrespective of the merits of these conclusions, envelopment of the capsid as it transits through the nuclear membrane is obligatory.

(*iii*) Production of infectious progeny virus is invariably accompanied by the irreversible destruction of the infected cell.

(*iv*) The herpesviruses examined to date are able to remain latent in their natural hosts. In cells harboring latent virus, the viral genomes take the form of closed circular molecules and only a small subset of viral genes is expressed.

Distribution in nature

Herpesviruses are widely disseminated in nature, and most animal species have yielded upon examination at least one herpesvirus. Table 1 lists the viruses identified at least on the basis of the architecture of the virus as belonging to the family *Herpesviridae*, and on the basis of serology, analyses of the DNA, or other methods as being a distinct herpesvirus species.

The naming of herpesviruses: definition of species

Summary of the procedure for naming herpesviruses

The procedure for naming herpesviruses is detailed in the 1981 report [187]. Briefly, a formal binomial nomenclature is not currently applied. The herpesviruses are named, with few exceptions, after the latinized name of the *family* of the host which in its natural setting harbors the virus. The exceptions are viruses isolated from humans, nonhuman primates, and from animals of economic importance in which a very large number of herpesviruses has been identified. When more than one virus is isolated from the same host, the viruses are given serial arabic numbers. Thus, herpesviruses isolated from human are designated as "human herpesviruses 1, 2 . . ." etc. Herpesviruses isolated from primates and the family *Bovidae* are designated by subfamily, and the name usually ends in "-ne", as for example, "pongine herpesvirus 1" for the chimpanzee herpesvirus, and "bovine herpesvirus 1" for infectious bovine rhinotracheitis virus. The names of other herpesviruses reflect the host family designation as for example "leporid herpesvirus 1" for the cottontail rabbit herpesvirus. Herpesviruses are numbered in order of discovery, not on the basis of relatedness.

To avoid confusion, if a herpesvirus designated by host family and serial number turns out to belong to another host family or to be a cell culture contaminant, that number is no longer used. In addition, the Herpesvirus Study Group in its 1981 report has specifically recommended against the use of designations such as type, subtype, etc. The Herpesvirus Study Group recognized that common names in use prior to the establishment of these rules will continue to be used.

Naming of herpesviruses implies recognition that the virus represents a new species. In some instances, the differences in the antigenic properties, structure of viral DNAs, and/or host range allow a clear differentiation between different herpesvirus species. For example human herpesviruses 1, 3, 4, and 5 (herpes simplex, varicella zoster, Epstein Barr viruses, and human cytomegaloviruses) are readily differentiated on the basis of antigenic properties, and of differences in base composition, size, sequence arrangement and homology of the DNAs. The HHV1 and HHV2 genomes are closely related and colinear; the viruses arising from recombination events between these two genomes are viable [189]. The basis for considering them as different species are (a) they are readily differentiated by serologic reagents and restriction endonuclease cleavage sites although the genomes of each species are highly polymorphic, and (b) the viruses occupy different ecological niches in that HHV1 generally infects people at a younger age than HHV2 (reviewed in [186, 189, 230]). HHV1

and HHV2 are not the only closely related herpesviruses classified as individual species. Thus a similar basis exists for separation of equid herpesviruses 1 and 4 associated with equine abortion and equine rhinopneumonitis, respectively [194, 217].

A consensus for definition of new species

The Herpesvirus Study Group has purposely avoided defining relatedness on the basis of percent matching of base pairs in as much as in the absence of complete sequences of the genomes the numerical value obtained from such determinations is dependent on experimental design. As a general principle, related viruses could be classified as distinct species if (a) their genomes differ in a readily assayable and distinctive manner across the entire genome (e.g., restriction endonuclease cleavage site patterns obtained with many enzymes) and not merely at a specific site (e.g., small number of genes or small number of restriction endonuclease sites) and (b) if the virus can be shown to have distinct epidemiologic and biologic characteristics. According to this definition, the HHV4 strains differing in the sequence of a small portion of their genome and currently named Epstein-Barr viruses types A and B (EBV-A and EBV-B [120]) would not be designated as distinct species and should be designated as variants A and B. On the other hand, should the HHV6 isolates differing in the patterns of cleavage with numerous restriction endonucleases [200] also differ with respect to epidemiologic and biologic properties, it would be appropriate to designate them as separate species, i.e., as human herpesvirus 6 and 8.

Classification

Current classification

The purpose of classifying viruses into subfamilies and genera is multifold. While a classification scheme is often used to depict evolutionary relatedness, it also serves a practical purpose of enabling the laboratory worker to predict the properties and identity of a new isolate. ICTV has approved the recommendation of its Herpesvirus Study Group that the members of the family *Herpesviridae* be classified initially into 3 subfamilies designated as *Alphaherpesvirinae, Betaherpesvirinae*, and *Gammaherpesvirinae*, on the basis of biologic properties in the first instance [187]. The classification is based on the evidence that notwithstanding many shared properties, the herpesviruses also vary greatly in their biologic properties. Some have a wide host species (human or animal) and cell range, multiply efficiently, and rapidly destroy the cells which they infect (e.g., HHV1, HHV2, suid herpesvirus 1, etc.). Others have a narrow host species and cell range (HHV4, HHV6). The multiplication of some herpesvirus appears to be slow (HHV5). While all herpesviruses remain latent in a specific set of cells, the exact cell in which they remain latent varies from one virus to another. For example, whereas latent HHV1 is recovered from sensory neurons, latent HHV4 is recovered from B lymphocytes. Herpesvirus differ with respect to the clinical manifestations of diseases they cause. A summary of the relevant properties of the members of the three subfamilies is as follows.

Alphaherpesvirinae

According to the 1981 proposal herpesviruses included into this subfamily should exhibit nonexclusively a variable host range, relatively short reproductive cycle, rapid spread in culture, efficient destruction of infected cells, and capacity to establish latent infections in sensory ganglia.

Betaherpesvirinae

Nonexclusive characteristics of the members of this subfamily is a restrict host range, a long reproductive cycle and slow spread of infection from cell to cell in culture. The infected cells frequently become enlarged (cytomegalia) and carrier cultures are readily established. The virus can be maintained in latent form in lymphoreticular cells and possibly in secretory glands, kidneys, and other tissues.

Gammaherpesvirinae

The experimental host range of the members of this subfamily is frequently but not exclusively limited to the family or order to which the natural host belongs. In vitro all members replicate in lymphoblastoid cells and some also cause lytic infections in some types of epithelioid and fibroblastic cells. Viruses in this group tend to be specific for either T or B lymphocytes, but exceptions may occur. In the lymphocyte, infection is frequently either at pre-lytic or lytic stage, but frequently without production of infectious progeny. Latent virus is frequently demonstrated in lymphoid tissue.

The ICTV also approved the Herpesvirus Study Group proposals to erect several genera based on DNA sequence homology, similarities in gene and sequence arrangements, and relatedness of important viral proteins demonstrable by immunologic methods (Table 2). While some genes (e.g., glycoprotein B [171, 229] and glycoprotein H [93]), are conserved among members of different subfamilies, nucleic acid and protein sequence homologies of less widely conserved genomic domains are particularly useful for the classification of viruses that are closely related (genera).

Current and future trends in herpesvirus classification

In principle, useful classifications are based on criteria that require a few or simple assays to determine and which are predictive of a whole range of properties and relationships. The biologic criteria used for classification of herpesviruses into subfamilies were based on simple measurements or observations that could be readily determined in numerous laboratories. Fortuitously, most herpesviruses assigned to the three subfamilies would have been assigned now to the same subfamilies on the basis of a wider range of objective criteria currently available; indeed, with few exceptions, the criteria proposed in 1981 yielded a scheme of relationships with mirrored that determined since by DNA sequence homology, gene organization, etc. The exceptions, however, are highly significant in that they indicate that the criteria used to align viruses to the three subfamilies are intrinsically unsatisfactory.

The key exceptions are the gallid herpesvirus 1 (GHV1, Marek's disease herpesvirus) classified in 1981 as a member of *Gammaherpesvirinae* and HHV6 which was not known at that time. In nature, GHV1 multiplies and produces cell free, infectious progeny in the keratinized cells of the chicken feather follicles. The virus multiplies in other cells in vivo and in a variety of cell lines in culture, but is retained in cells and not readily released in infectious form. The classification of the virus as a member of the *Gammaherpesvirinae* reflected the observation that the virus caused tumour-like growths in chickens, the tumours were of lymphoid type, and that viral genomes were present and expressed in cells contained in those tumours. Current data indicate that the gene arrangement resembles that of *Alphaherpesvirinae* rather than that of *Gammaherpesvirinae* [38]. It could be argued that the initial classification was erroneous, that it ignored properties which resembled those of *Alphaherpesvirinae* (e.g., growth in fibroblasts, relatively rapid spread in culture notwith-

Table 2. List of genera within the family *Herpesviridae*

Subfamily/ genus	Viruses	Common name
Alphaherpesvirinae		
Simplexvirus[a]	human herpesvirus 1	herpes simplex virus 1
	human herpesvirus 2	herpes simplex virus 2
	bovine herpesvirus 2	bovine mammillitis
	cercopithecine herpesvirus 1	B Virus
Varicellovirus[a]	human herpesvirus 3	varicella-zoster virus
	equid herpesvirus 1	equine abortion virus
	bovine herpesvirus 1	infectious bovine rhinotracheitis virus
	suid herpesvirus 1	pseudorabies virus
Betaherpesvirinae		
Cytomegalovirus[a]	human herpesvirus 5	human cytomegalovirus
Muromegalovirus[a]	murid herpesvirus 1	murine cytomegalovirus
Roseolovirus[b]	human herpesvirus 6	
	human herpesvirus 7	
Gammaherpesvirinae		
Lymphocryptovirus[a]	human herpesvirus 4	Epstein-Barr Virus
	cercopithecine herpesvirus 12	baboon herpesvirus
	cercopithecine herpesvirus 14	African green monkey, EBV like virus
	cercopithecine herpesvirus 15	rhesus monkey EBV like virus
	pongine herpesvirus 1	chimpanzee herpesvirus
	pongine herpesvirus 2	orangutan herpesvirus
	pongine herpesvirus 3	gorilla herpesvirus
Rhadinovirus[a]	ateline herpesvirus 2	herpesvirus ateles 2
	saimirine herpesvirus 2	herpesvirus saimiri 2
	bovine herpesvirus 2	
	alcelaphine herpesvirus 1	virus of malignant catharral fever
	murid herpesvirus 1	mouse herpesvirus strain 68

[a] Approved by International Committee on Taxonomy of Viruses
[b] Proposed name for genus

standing its cell associatedness, etc.) and took into account the one criterion which was not among those listed for classification, namely that none of the known viruses which comprise the *Alphaherpesvirinae* commonly cause tumours in their natural hosts and remain associated with the tumour cells.

The ambiguity which surrounds the initial classification of GHV1 as a *Gammaherpesvirus* is less apparent in the case of HHV6. By the 1981 criteria, HHV6 should be assigned to the *Gammaherpesvirinae* on the basis of its tropism for lymphocytes. However, on the basis of sequence homology and gene organization, HHV6 is related to HHV5 and more properly belongs to the *Betaherpesvirinae*. It is worth noting that lymphocytes are fully permissive to HHV6 whereas gammaherpesviruses generally cause non-productive or latent infection in this cell type. Our knowledge of the biology of HHV5 has also undergone a change in that we are not as likely to exclude the association of this virus with lymphoid cells as was the case in 1981.

The problem now facing the Herpesvirus Study Group is the selection of objective criteria that match the 1981 criteria in simplicity and usefulness, but lack the ambiguity to

which the 1981 criteria are subject. The objective criteria that have been proposed for the classification of herpesvirus subfamilies are (*i*) conservation of genes and gene clusters (e.g., DNA polymerase, glycoproteins B, C, and H, single strand DNA binding protein, major capsid protein, etc.) (*ii*) the arrangement of gene clusters relative to each other; (*iii*) the arrangement of the terminal sequences involved in packaging of the viral genome; and (*iv*) the presence and distribution of nucleotides that are subject to methylation [42, 56, 58, 60, 92, 125, 167].

The selection of suitable criteria depends on the purpose for collecting taxonomic data. The objectives of herpesvirus taxonomy are multifold. At one level, the taxonomy must provide a quantitative measure of the relatedness of the different herpesviruses to each other from which one can infer an evolutionary tree. At the other extreme, not all herpesviruses rampant in nature have been identified and taxonomy must also serve the purely utilitarian function of assisting those involved in the isolation of new viruses to predict biologic properties in the same fashion that anatomic characteristic serve to identify insects and plants and biochemical and morphologic properties identify bacteria.

Taxonomic data useful for the erection of an evolutionary tree must be based on nucleotide sequence of viral genomes. At present the sequence of at least 10 herpesviruses is either known or nearing completion (e.g., HHV1–6, saimirine herpesvirus 2, equine herpesvirus 1, and ictalurid herpesvirus 1). Although additional herpesvirus genomes are likely to be sequenced, it is not likely that the number of genomes analyzed in this fashion will keep pace with the discovery of new herpesviruses. On the other hand, although the number of sequenced herpesvirus genomes represents less than 10% of the known herpesviruses, the data generated from this collection may suggest limited domains of other herpesviruses which must be sequenced to place them in the appropriate taxonomic groups. The central question is the nature of these domains. A more complex problem is the identification of nucleotide or protein sequence correlates of biologic properties of the various herpesviruses.

At present arguments can be marshalled to reject each of the criteria proposed to date, and a few examples may suffice. For example, it can be argued that highly conserved genes are responsible for the common properties of herpesviruses, and hence analyses of the sequence of their products might provide clues to their evolutionary relationships. Inasmuch as the object of the taxonomy of herpesviruses is to differentiate among a family of viruses which share very obvious structural and replicative properties and yet show considerable biologic diversity, the key question is whether evolutionary divergence of the conserved genes could be prognostic of biologic diversity.

Another proposal enumerated above centered on the polarity and colinearity of conserved gene clusters. The argument is that such arrangements are likely to have evolved gradually and may reflect evolutionary relationship more precisely than gene product sequence which might be under selective pressure imposed by the ecological niche of the virus. The counter argument is that gene rearrangements arise through intermolecular and intramolecular inversion and recombination events that are known to occur among herpesviruses and that such arrangements while useful in defining potential relationships may not arise solely by divergent evolution and also may not be prognostic of biologic properties.

It can be argued also that each herpesvirus occupies a unique ecologic niche and that the genes prognostic of biologic diversity are genes unique to specific ecologic niches, i.e., replicating or remaining latent in specific cells or organs, but not conserved among all herpesviruses. Such genes could be predicted to be dispensable for growth of cells in culture.

The size of this group of genes is reflected in the observation that 38 of the 73 diverse open reading frames of HHV1 can be deleted without abolishing the capacity of the virus to multiply at least in some cells in culture ([189] and B. Roizman, unpubl. data). The function of these deletable genes is largely unknown, and most of them are not conserved across different subfamilies. To illustrate the point in the context of GHV1, the conserved genes, i.e., those that are homologous and nearly colinear with those of HHV3 [38] are not the domains expressed during latency or in transformed cells. The expression of GHV1 in cells harboring latent virus is quite different from that of HHV3 [218]. Delineation and evolutionary relatedness of genes responsible for biologic properties may be a more significant criterion for both evolutionary relatedness and classification than the arrangement and evolution of genes conserved throughout the family *Herpesviridae*. The problems with this approach are also numerous. Not all "dispensable" or non conserved genes are necessarily prognostic of biologic activity and the function of most of the non conserved genes is not known.

The present position of the Herpesvirus Study Group is as follows: (*i*) Nucleotide sequence data are necessarily the basis of the taxonomy of the family *Herpesviridae*. The central issue is the identification of the correlates which must be culled from such data for a truly useful taxonomy. (*ii*) The Study Group as well as the herpesvirus community is confronted with a large number of options which may eventually lead to the construction of an evolutionary tree, but none provide as yet clear correlates between predicted herpesvirus protein sequence and biologic properties. (*iii*) No single property is likely to form the basis of a truly useful and enduring taxonomy of herpesvirus. The key properties which jointly are likely to form the basis of a future taxonomy are the evolutionary divergence of conserved genes, the identification of nonconserved genes that best correlate with the ecologic niches of the diverse herpesviruses, and the gene polarity and clustering within the viral genomes. The exponential increase in the generation of data on herpesviruses suggests that the information required for a taxonomy based on more objective criteria than the one currently available may not be long in coming.

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