Animal Papillomaviruses

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Introduction

Systematic studies as well as anecdotal observations suggest that all mammals, some (or all) birds, and probably some other vertebrates and even nonvertebrates are infected by papillomaviruses (PVs). Historically, these observations were made by pathology examination, electron microscopy, or immunohistochemistry with polyclonal antibodies against the highly conserved L1 protein. In the last 15 years, these studies were strengthened by detection of the viral genome by Southern blotting, cloning of the whole PV genome and cloning of partial PV genomes amplified by the polymerase chain reaction (PCR). This direct evidence from molecular cloning is much preferable, as nucleotide sequence information is necessary for PV typing and nomenclature, just as it is in the case of human PVs (HPVs).

The depth of studies of animal PVs varies enormously. At one extreme is bovine PV type 1 (BPV-1), which became a principal model system for research into the molecular biology of PVs and the object of hundreds of publications. At the other extreme are anecdotal reports of lesions in wild, captive or domestic animals, whose pathology suggested a possible PV-related etiology. This short review does not attempt to cover this wide array of publications, but concentrates on those animal PVs for which genomic sequence information is available.

Reviews about animal PVs

Animal papillomaviruses have been studied under a variety of little related aspects. Selective topics are covered in the following reviews:

(i) Detection and isolation of PVs and PV lesions in various vertebrates (46, 48).

(ii) Epidemiology of ungulate PVs in domestic animals, and laboratory studies of ungulate PVs in rodents (18).

(iii) Taxonomy, phylogeny, and sequence analysis (8–10, 48, this compendium and its predecessors).

(iv) BPV-1 and CRPV as model systems for the molecular biology of PVs (17,25).

(v) Animal PVs as model systems for cancer and vaccination studies (2,3,5–7,19).

Nomenclature and definition of types

Different papillomavirus types are designated by the abbreviation "PV" which is (i) preceded by one or two letters indicating the host species, and (ii) followed by a number whenever multiple PV types are found in the same host species, e.g. BPV-4 for bovine papillomavirus type 4. There is no formal agreement how exactly to apply these specifying codes.

As to the prefix, single or double capital letters have been used to identify the common name of the host species, e.g. BPV-1, or CRPV (for cottontail rabbit PV). Sometimes the second letter points to the site where lesions occur, e.g. COPV (for canine oral PV). Alternatively, a capital and a lower case letter may abbreviate the host's scientific name, e.g. MnPV (for *Mastomys natalensis* PV). The latter is probably the most desirable procedure, as it would be consistent with the well established taxonomy of the host (48). Just like in other parts of biological research, it may be unfeasible to eliminate historically widely used common names.

A taxonomic system following numbers has been formally defined for HPVs, and two independent HPV isolates are defined as separate types and given unique numbers, when the nucleotide sequences of their L1 genes differ by at least 10% (52). This arbitrary definition has proven to be very successful in practice. On the one hand, most different HPV genomes have been found in multiple independent

isolates to have very similar sequences. On the other hand, the nucleotide sequence of most previously described HPV types is more than 10% dissimilar from any other type, and only a few exceptional isolates are more closely related (for discussions of these subjects see 9,16,36,44). The presently available nucleotide sequences suggest that it is appropriate to use this definition for animal PVs as well, because all sequenced isolates are either very similar to one another, thus belonging to the same type, or at least 10% dissimilar from one another, indicating a separate type. An exception may be the Pigmy Chimpanzee PV and the Chimpanzee PV, whose partial L1 sequences are only approximately 9% dissimilar (12).

The description of animal PVs

The taxonomic diversity and the epidemiology of animal PVs has been researched mostly anecdotally rather than systematically. Nevertheless, it is apparent that many or even most animals are infected by unrelated PVs. In addition, all of the six extensively studied host species—humans, Rhesus monkeys, Colobus monkeys, rabbits, cattle, and sheep—carry multiple PV types. As there are roughly 15,000 species of mammals and birds, all likely host species, one can speculate that there could exist more than one hundred thousand different animal PV types.

Among this great lot, only about sixty have been dealt with in scientific publications. They can be placed into four categories, depending on whether (1) the genomic clone and nucleotide sequence are both available to the public, (2) the genomic clone is available but the nucleotide sequence unpublished, (3) the genome has been cloned but neither the clone nor the nucleotide sequence are presently available, and (4) PVs which are presumed to exist from pathological, immunohistochemical or other indirect observations, but whose genome has never been cloned.

(1) Table 1 summarizes those 34 animal PVs that have been completely (20 PVs) or partially (14 PVs, namely RhPV-a to m, MfPV-a, and ChPV) cloned and sequenced. L1 sequences for our standardized database are available for 33 of these, while only E6 sequences are available for MmPV (see Fig. 1 and below).

(2) Two additional PV genomes from cutaneous lesions of domestic horses (EcPV, 34) and oral lesions of domestic rabbits (ROPV, 32) are cloned and available at the Reference Center for Human Pathogenic Papillomaviruses in Heidelberg, but nucleotide sequences are not yet available.

(3) Two further animal PV types have been cloned, but neither the genomes nor the genomic nucleotide sequences are presently generally accessible. These are a cat PV (FdPV, 53) and a PV from an African Grey Parrot (33).

(4) Cutaneous papillomas and other epithelial lesions reminiscent of a PV etiology have been described from approximately 20 additional animal species. These host species include representatives of most orders of mammals, for example marsupials, dolphins, and elephants, as well as a few species of birds, reptiles, fish, and even molluscs. In only a few of these examples is there evidence for infection by (probably undescribed) PVs based on Southern blotting or immunohistochemical staining with polyclonal anti-L1-antisera. For the rest the evidence is based on histopathological observations, and a PV association is far from certain. These papers have been reviewed (46), and the PVs that fall into this category are not treated here.

Stability of PV genomes

Comparisons between viral genomes would be incomplete without taking into account the time over which genomic diversification arose. Viral phylogenetic studies are very much dominated by the large proportion of research on RNA viruses, for example on the human immunodeficiency virus type 1 (HIV-1). Observations about RNA viruses frequently give rise to the generalization that viruses evolve very quickly. While this is true for RNA viruses, it does not apply to DNA viruses in general and to PVs in particular. The extent of genomic diversity among all known PVs is comparable to the genomic diversity among subtypes of HIV-1. Whereas diversification in the latter case may have taken merely part of a century, it is likely that diversification among PVs took millions of years. This suggests that PV evolution proceeds more slowly, by approximately five orders of magnitude, than evolution of rapidly evolving RNA viruses.

Table 1 Thirty four animal papillomavirus types, whose complete or partial genomic clones and nucleotide sequences, are available.

Host	Designation	Source	Reference
Chimpanzee (*Pan troglodytes*)	ChPV	oral cavity	12
Pigmy Chimpanzee (*Pan paniscus*)	PCPV	oral cavity	51
Rhesus macaque (*Macaca mulatta*)	RhPV-1	penile carcinoma	38
	RhPV-a–m	genital scrape	8
Long-tailed Macaque (*Macaca fascicularis*)	MfPV-a	genital scrape	8
Abyss.Colobus monkey (*Colubus guerezae*)	CgPV-1	papilloma (penile)	35
	CgPV-2	papilloma (head)	24,40
Domestic dog (*Canis familiaris*)	COPV	oral carcinoma	47
Domestic cattle (*Bos taurus*)	BPV-1	fibropapilloma	46
	BPV-2	fibropapilloma	46
	BPV-3	papilloma (skin)	46
	BPV-4	papilloma (esophagus)	46
	BPV-5	fibropapilloma	46
	BPV-6	papilloma (teat)	46
Deer (*Odocoileus virginianus*)	DPV	fibropapilloma	14
European Elk (*Alces alces*)	EPV	pulmon. fibromatosis	29
Reindeer (*Rangifer tarandus*)	RPV	fibropapilloma	27
Domestic Sheep (*Ovis domesticus*)	OvPV-1	papilloma	54
	OvPV-2	fibropapilloma	22
Cottontail Rabbit (*Sylvilagus floridanus*)	CRPV	papilloma	46
Harvest mouse (*Micromys minutus*)	MmPV	papilloma	34a
Multimammate Rat (*Mastomys natalensis*)	MnPV	papilloma and keratoacanthoma	30,49
Chaffinch (*Fringilla coelebs*)	FPV	papilloma	28

The concept of a slow speed of PV evolution is based on the following evidence: (i) PVs use the same high-fidelity enzyme machinery for replication as their eukaryotic hosts (50). (ii) PVs replicate slowly, because their multiplication is linked to the division of the infected epithelial host cell. (iii) The relationship and distribution of variants of several HPV types suggest that these already existed at the time when humans originated as a species several hundred thousand years ago (16,23,36). These data suggest that diversification of the most variable parts of HPV genomes occurs at a maximal rate of 0.25% over a period of ten or twenty thousand years. (iv) Several animal PVs, in particular BPV-1, have been isolated from domestic animal populations remote from one another and at different points in time with nearly identical nucleotide sequences (1,39).

Host species specificity of PVs

So far, no animal PV has been detected in humans, and no HPV type has been found in any animal species (though it should be recognized that HPV-13 and chimpanzee PVs are very close in their amino acid sequences). This observation is surprising given the frequent mutual exposure between humans and animals as game, pets, and livestock. Such apparent species specificity may be due to highly specific molecular interactions between viral and host proteins (42). While this hypothesis has never been rigorously tested to our knowledge, there are informal reports that vaccine developers can infect animals with human PVs; when these results become better known, our assessment of primate host specificity will become clearer. There are extensive observations, that BPV-1 and BPV-2 can infect diverse species of livestock, namely cattle, horse, donkey and sheep. This argues against mechanistic barriers to the transmission of the ungulate fibropapillomaviruses. This may be a recent result of high density cohabitation of domestic animals, as species specific PVs have been found in sheep and horses as well.

A Phylogenetic Tree of 34 Animal PVs and 77 HPV Types

The relationship among different PVs can be established by comparison of homologous nucleotide sequences through algorithms based on cladistic assumptions. The output of such evaluations is visualized as phylogenetic trees. Phylogenetic trees have been calculated (i) by three independently working research groups (9,48, and the group of G. Myers in this compendium series), (ii) based on the alignment of E6, E1, or L1 sequences, and (iii) under application of algorithms based on very different mathematical models. One notes with some satisfaction that the outcome of these different approaches has generated trees with very similar topologies, and that the differences are in regard to minor aspects of the topology. The tree shown in Fig. 1 is a representative phylogenetic tree based on the alignment of a well studied 291-bp-segment in the 3′ part of the L1 gene. The database for this segment includes presently 110 PV types, namely 77 HPVs, 32 mammalian PVs, and 1 bird PV. The relationship of 1 additional PV, MmPV, is indicated based on E6 sequences.

The general features of these trees are as follows: All HPV types (except HPV-1, HPV-41, and HPV-63), form two major branches (referred to as supergroups), that are designated as genital and epidermodysplasia verruciformis HPVs, respectively, independent of the actual associations of these HPVs and specific lesions. As to animal PVs, the most important findings concerning these two major branches are that all PVs from ape or monkeys are associated with them, and that so far no non-primate PV is related to them. Interestingly, the only two ape PVs, chimpanzee PV (ChPV) (12) and pigmy chimpanzee PV (PCPV) (51) are part of a minor branch including HPV-6, HPV-11, and HPV-13), while the fourteen PVs from monkey species are not intermixed with HPVs, but form minor branches of their own (8), possibly reflecting close or more distant relationship of their hosts.

The only other animal PV which is topologically associated with HPVs is the canine oral PV (COPV), a distant relative of HPV-1 and HPV-63. HPV-41 and the cottontail rabbit PV (CRPV) are included in a branch with these three PV types in some but not all trees, indicative of a remote relationship among these five viruses.

Two additional major branches are formed by eight different fibropapillomaviruses isolated from five different species of ungulates, and by three different cutaneous bovine PVs, namely BPV-3, BPV-4, and BPV-6.

Figure 1. The relationship among 34 animal PV and 77 HPV types. The positions of animal PVs or clusters of animal PVs are highlighted by arrows. The tree is based on a neighbor-joining phylogeny calculated from the alignment of a 291 bp segment of the L1 gene. For details of this procedure and the source of the nucleotide sequences, see refs. 8–10. The nucleotide sequence of the Chimpanzee PV (12) is unpublished, but has been made confidentially available. Abbreviations: BPV, bovine PV; CgPV, Colobus monkey PV; ChPV, Chimpanzee PV; COPV, Canine oral PV; CP, untyped partial HPV clone; CRPV, Cottontail rabbit PV; DPV, Deer PV; EPV, European elk PV; FPV, Chaffinch PV; HPV, human PV; LVX, untyped partial HPV clone; MM, untyped partial HPV clone; MmPV, *Mycromys natalensis* PV; MnPV, *Mastomys natalensis* PV; OvPV, Ovine (sheep) PV; PCPV, Pygmy chimpanzee PV; RPV, Reindeer PV; RhPV, Rhesus monkey PV.

Two PVs from rodents, MmPV and MnPV, do not show a close relationship among one another nor to any other animal PV. The only presently sequenced bird PV, FPV, is topologically even more isolated.

It has been claimed that a cat PV (FdPV) is related to the HPV-1/41/63/COPV/CRPV branch (11), that a horse PV (EcPV) is related to the fibropapillomaviruses (48), and that a rabbit oral PV (ROPV) is related to CRPV (48). As the nucleotide sequences have not been published, general acceptance of these evaluations has to await release of these data. If validated, these claims may further support the idea that the relationship among PVs reflects to a degree the relationship among their hosts. Following the same hypothesis, it will be of great interest to study the relationship of the Chaffinch PV (FPV) with the only other known bird PV from African Grey Parrots (33).

Conflicting views about "coevolution"

The specificity of most PV types for a single host species suggests the postulate that PVs evolved together with their host. For this phenomenon, we proposed the descriptive term "host-linked evolution" (8,9), because the term "coevolution", which is sometimes used in the PV literature (48) has been earlier defined to describe mutual selective pressure between host and parasite (15,21). It does not seem plausible to us that such a mutual influence exists in the case of PVs and their host.

The slow change of PV nucleotide sequences suggests that PVs already existed in a similar genomic form to that observed today several million years ago, when host taxa from the level of the phylum down to species or populations were forming. This hypothesis is supported by the observation of topological structures in the phylogenetic tree of PVs that reflect the relationship among the various host species:

(i) The isolated position of the only known bird PV,

(ii) clustering of all ungulate PVs in two major branches,

(iii) clustering of all non-human primate PVs with HPVs,

(iv) clustering of all known Macaque PVs in separate minor branches to the exclusion of any HPVs (8),

(v) the very close association among the only two known ape PVs with specific HPV types (12,51),

(vi) phylogenetic trees of variants of HPV-16 and HPV-18 with topological similarities to the phylogenetic trees of the ethnic groups of the infected patients (16,36).

However, there is no reason to believe that host speciation "drives" PV evolution, nor does one presently have to postulate mechanistic incompatibilities between virus and host soon after speciation of the latter. More likely is a model whereby transmission between different vertebrate species is an improbable event given the apparent requirement of close physical contact for PV transmission, which may rarely occur in vertebrates in the wild. The reproductive isolation and speciation of host populations may therefore isolate PV populations from one another with viral diversification ensuing subsequently.

While host speciation certainly prevents extensive intermingling of PV populations, establishment of new PV types does not require host speciation, but can occur independently. The data include:

(i) the large number of PV types in humans, rhesus macaques, and cattle,

(ii) multiple minor branches of PVs in Rhesus macaques, suggestive of multiple PVs in some phylogenetic ancestor of these monkeys,

(iii) a genital PV type and an epidermodysplasia verruciformis-like PV type in Colobus monkeys, suggestive that both PV lineages existed in a common ancestor of Colobus monkeys and humans (10).

As PVs can speciate, *i.e.*, evolve new types or other taxa, before, at the time of, or after speciation of the host, it is probably not very useful to try to reconstruct PV evolution in strict concordance with host evolution, as has been suggested (48).

Myers and colleagues have advocated the potential of cross-species transmissions (zoonotic transmissions) as a possible source of evolutionary jumps (31), citing the close relationship of HPV-13 and

PCPV (51), which are designated as "close" types due to the lack of major changes in the amino-acid sequences of their PV's proteins. From what was said above it is clear that we intepret the same sequence data (and the inclusion of the Chimpanzee PV in the HPV-13/PCPV pair) as originating from the close relationship of the hosts, i.e., the fairly recent evolutionary split between humans, chimpanzees and pigmy chimpanzees.

Genomic and biological idiosyncrasies of animal PVs

PVs have the same genomic organizations of open reading frames and intergenic regions that are apparently homologous: E6-E7-E1-E2/E4-(E5)-SIR-L2-L1-LCR. (SIR, short intergenic region; LCR, long control region). With the exception of E5, all of these genes of different PVs are homologous to one another, as evidenced by the extensive similarities in intertype-alignments published in this compendium and its precursor volumes. E5 exists only in genital HPVs and in the BPV-1 related fibropapillomaviruses. Although the E5 genes of both supergroups encode highly hydrophobic membrane proteins with similar molecular properties, there is no indication from sequence studies that these two protein families are homologous.

BPV-4 (and the relatives BPV-3 and BPV6) constitute the only major exception to the standard gene layout of PVs by lacking the homologue of an E6 gene. In place of E6 their genomes contain an open reading frame termed E8, which encodes a hydrophobic membrane protein with functional similarities to E5 proteins (13,20). However, there is no indication that the BPV-4 E8 gene may be homologous to either the E5 gene of genital HPVs, or to the E5 gene of fibropapillomaviruses. Presently a common origin of the E5 genes of genital HPVs, the E5 genes of fibropapillomaviruses and the BPV-4 E8 gene is not supported by sequence studies, and all three families of genes might have originated independently from one another and may constitute examples of convergent evolution.

Another major idiosyncrasy has been detected in the canine oral PV (COPV), which has a 1.5 kb non-coding region between E2 and L2 in the same position where all other PVs have a more than 10-fold shorter non-coding region (11). No function is known to be associated with this sequence, except transcription termination signals of the early genes similar to those of all other PVs. The sequence has no similarity to any other sequence in the GenBank database. As COPV is remotely related to HPV-1 and HPV-63, which do not have such a large intergenic region, one may speculate that this sequence is not a prerequisite for idiosyncrasies of the COPV lifecycle, but may have originated by a recombination event, being retained as it was not detrimental.

It should be stressed that the supergroup of fibropapillomaviruses is the only one with members that also infect mesenchymal cells and fibroblast cell cultures. Neither extensive molecular research into BPV-1 gene functions, nor sequence analyses have pointed so far to the origin of this unusual biology.

Animal PVs in medical research

The existence of seven homologous genes in every animal and human PV suggests similar structures and functions of the encoded proteins. Consequently, immunological studies of animal PVs or drug screens targetting molecular properties of specific animal PV proteins should play a useful role in medical research into HPV associated human disease and treatment (3). The most visible examples include the use of BPVs (5–7) and CRPV (26,41) for immunological studies, a CRPV-based model permitting the study of the consequences of (molecularly altered) PV DNA injected into rabbit skin (4,45), and serological studies of RhPV-1 as a model for genital HPVs (37,38). This is a surprisingly small number of animal PV-based models for important human diseases, and it has to be hoped that these systems may gain more widespread use than is presently the case.

Future prospects

Some of the presently well known animal PV types will continue to play a major role as model systems for the study of molecular mechanisms and immunological properties of PVs. On the other side, information about novel animal PVs is growing very slowly, and phylogenetic comparisons may temporarily plateau once the nucleotide sequences of EcPV, FdPV, ROPV, and the African Grey Parrot

PV are published, the only animal PVs, that are presently isolated but not yet completely studied. When one considers the large amount of work that is required to isolate and completely sequence a single novel PV type, it is unlikely, that this research will attain high priorities, although PVs fascinate as being the best studied model system for the evolution of DNA viruses. We hope and propose that more economical PCR based studies, as done for the detection of novel monkey viruses (8), may permit us to expand our knowledge of the diversity of animal PVs in spite of funding restrictions.

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