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Review Article

Why HPV16? Why, now, HPV42? How the discovery of HPV42 in rare cancers provides an opportunity to challenge our understanding about the transition between health and disease for common members of the healthy microbiota

Ignacio G. Bravo*, Sophia Belkhir, Philippe Paget-Bailly

Laboratory MIVEGEC (Univ Montpellier, CNRS, IRD) French National Center for Scientific Research (CNRS), Montpellier, 34394, France
*Corresponding author. National Center for Scientific Research (CNRS), Laboratory MIVEGEC, Team VIROSTYLE, 911 Avenue Agropolis, Montpellier, 34394, France. E-mail: ignacio.bravo@cnrs.fr
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Abstract

In 2022, a bioinformatic, agnostic approach identified HPV42 as causative agent of a rare cancer, later confirmed experimentally. This unexpected association offers an opportunity to reconsider our understanding about papillomavirus infections and cancers. We have expanded our knowledge about the diversity of papillomaviruses and the diseases they cause. Yet, we still lack answers to fundamental questions, such as what makes HPV16 different from the closely related HPV31 or HPV33; or why the very divergent HPV13 and HPV32 cause focal epithelial hyperplasia, while HPV6 or HPV42 do not, despite their evolutionary relatedness. Certain members of the healthy skin microbiota are associated to rare clinical conditions. We propose that a focus on cellular phenotypes, most often transient and influenced by intrinsic and extrinsic factors, may help understand the continuum between health and disease. A conceptual switch is required towards an interpretation of biology as a diversity of states connected by transition probabilities, rather than quasi-deterministic programs. Under this perspective, papillomaviruses may only trigger malignant transformation when specific viral genotypes interact with precise cellular states. Drawing on Canguilhem's concepts of normal and pathological, we suggest that understanding the transition between fluid cellular states can illuminate how commensal-like infections transition from benign to malignant.

Keywords: papillomavirus; diversity; ecology; evolution; virome; microbiote; infection and cancer; cell type; phenotype; virus–host interactions; genotype-to-phenotype; phenotype-to-environment

From the viral theory of cancer to the most oncogenic biological agent for humans

Research in the first half of the twentieth century solidly established that chronic infections by certain viruses could cause tumours, as pioneered by Rous (Rous 1911) and by Fujinami (Fujinami and Inamoto 1914). Indeed, before the paradigm shift towards a genetic component of cancer susceptibility, the viral theory of cancer '*aspired to explain most or all types of the disease as being induced by viruses*' (Duran-Reynals 1953). The viral aetiology of human warts had been established through classic filtration and inoculation experiments, moving the authors to propose that '*if a filtrable virus can produce marked epithelial hypertrophy, may not this have a bearing on the growth of epithelium in other tumors, for example, malignant tumors?*' (Wile and Kingery 1919). The ability of rabbit papillomaviruses to induce warts in wild rabbits and tumours in domestic rabbits was consistently demonstrated later (Shope and Hurst 1933). The consensus in the 1960s classified papillomaviruses of rabbits and humans, polyomaviruses (PyVs) of mice, and vacuolating viruses of monkeys, together into a papova virus group, as they all shared morphological and genomic similarities and all of them '*produce latent and chronic infections in their natural hosts, and all are tumorigenic in their natural or other host species, or both*' (Melnick 1962).

In this intellectually favourable context, zur Hausen (1976) pinpointed that cervical cancer presented an epidemiological pattern similar to that of genital warts and condyloma acuminata, suggesting that the same virus could be responsible for both clinical presentations. This was at the time a risky hypothesis, because even if a viral aetiology had been proposed for genital warts [(Ciuffo 1907), cited by (Karamanou et al. 2010)], no papillomavirus (PV) DNA had been detected in genital warts, including attempts by the group of zur Hausen himself (zur Hausen et al. 1974a, DeLap et al. 1976). The origin of the inconsistency was the unexpected diversity among human PVs (HPVs), as at the time the '*human papova (wart) virus*' was thought to be an individual, single entity (Rowson and Mahy 1967). However, the fever for viral isolation and characterization rapidly revealed the large genetic heterogeneity among HPVs (Gissmann and zur Hausen 1976,

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Gissmann et al. 1977): (i) the genome of HPV1 was characterized in 1977 (Orth et al. 1977); DNA from a novel virus, HPV6, was eventually identified from a condyloma acuminata (Gissmann and zur Hausen 1980); and the genome of HPV16, which was not responsible for condyloma acuminata but turned to be the most oncogenic biological agent to humans, was identified (Dürst et al. 1983, 1987) and sequenced (Seedorf et al. 1985) shortly thereafter. It is now well established that a handful of HPVs are oncogenic for humans (Walboomers et al. 1999, Arbyn et al. 2014), and that they are globally responsible for around 5% of all new cancer cases every year (de Martel et al. 2020). The current diversity estimates, based on targeted as well as on broad metagenomic surveys, suggest that there exist around 800 distinct HPV genotypes (Arroyo Mühr et al. 2021), extremely diversified, and that do not share a single, exclusive recent common ancestor (Willemsen and Bravo 2019).

The twisted road between genotype and phenotype in papillomaviruses

PVs display a conserved, syntenic core set of early and late open reading frames (ORFs). The *l1* ORF, encoding for the main capsid protein, displays the lowest ratio in amino acid substitutions over nucleotide substitutions (Mengual-Chuliá et al. 2016), and pairwise genetic distances between *l1* sequences display a multimodal distribution that can be used to define taxonomic categories (de Villiers et al. 2004). The finest-grain category for PV taxonomy recognized by the International Committee for the Taxonomy of Viruses is the viral species, which comprises PV genomic sequences sharing between 71% and 89% nucleotide identity within the complete *l1* ORF (https://ictv.global/report/chapter/papillomaviridae/papillomaviridae). However, for the PV research community the clinically relevant taxonomy level is rather the PV type, a category that comprises viral genomic sequences sharing between 90% and 98% nucleotide identity within the complete *l1* ORF (de Villiers et al. 2004, Van Doorslaer 2022). Indeed, types within a same PV viral species can display large biological differences. A first, clinically important example of large quantitative differences among types within a PV species is AlphaPV-species-9, which includes seven HPVs, with a close evolutionary relationship, similar gene composition, and with similar tropism (Willemsen and Bravo 2019) but that span a large variation in oncogenic potential, the extremes being HPV16, the most oncogenic biological agent to humans, 20 times more prevalent in cervical cancers than in normal cervical samples, and HPV67, closely related to it and recognized as possibly carcinogenic, but with similarly very low prevalence in cervical cancer and in normal cervical samples (HPV Information Centre). A second cogent example of the large phenotypic diversity for diseases associated to closely related HPVs is AlphaPV-species-10, which includes seven HPVs and two nonhuman primates PVs. Members of this species comprise HPV6 (Gissmann and zur Hausen 1980) and HPV11 (Dartmann et al. 1986), sister viruses associated to genital warts and to respiratory recurrent papillomatosis, but also HPV13 (Pfister et al. 1983), PpanPV1 infecting bonobos (Van Ranst et al. 1991), and PtroPV1 (Scinicariello et al. 1997) infecting chimpanzees, the latter three associated to focal epithelial hyperplasia in their respective host species. Finally, a third example of distantly related HPVs associated to a similar clinical presentation is focal epithelial hyperplasia. This proliferative disease displays a particular epidemiology in terms of human genetic background and geographical distribution (Archard et al. 1965), and seems to be associated to two, only distantly related viruses: HPV32, member of AlphaPV-species-1 (Beaudenon et al. 1987b) and HPV13, member of AlphaPV-species-10 (Pfister et al. 1983).

But for HPVs, the differences between evolutionary and genomic relatedness on the one hand and clinical presentation of the infection on the other hand are also noticeable at the shallower taxonomic level of viral variants. For PVs, viral variants comprise viral genome sequences sharing above 98% identity, usually evaluated across the complete genome (Burk et al. 2013), although the distribution of polymorphisms is not homogeneous among ORFs (Mengual-Chuliá et al. 2016, Mirabello et al. 2017). Despite this very close genetic relationship, variants within the same HPV type present differences in geographical distribution and prevalence (Eschle et al. 1992, Xi et al. 1997, Yamada et al. 1997, Clifford et al. 2019), epidemiology (Zehbe et al. 1998, Villa et al. 2000, Sichero et al. 2007, Mirabello et al. 2016, 2017), or function (Stoppler et al. 1996, Hu et al. 2002, Sichero et al. 2005, Asadurian et al. 2007, Lace et al. 2009). A fraction of these biological differences between variants can be accounted for by a *virus genotype* × *host genotype* interaction, in which the parallel evolution of viruses and hosts would have resulted in differences of variant prevalence and of association with disease (Ong et al. 1993, Xi et al. 2006). Further, episodes of recombination, isolation, and transmission between related hosts could have disrupted virus–host parallel evolution and lead to differential cancer risk (Gottschling et al. 2011), as proposed for the transmission of specific HPV16 variants from Neanderthals to anatomically modern humans (Pimenoff et al. 2017). Another fraction of the biological differences between variants is probably related to specific *virus genotype* × *cell (pheno)type* interactions, including specific internal cues (*e.g.* biochemical status or cell cycle), changes across cell ontogeny (*e.g.* keratinocyte differentiation), and/or external cues (*e.g.* stress signals, tissue homeostasis, or paracrine regulation). Overall, even closely related variant genotypes may be expressed differently in different cellular geno/phenotypes, resulting in differences in the natural history and eventually in the clinical presentation of the infection. Such interactions have been extensively documented for the differential prevalence of HPV6 and HPV11 variants in genital warts (Flores-Díaz et al. 2017a, b) and in respiratory recurrent papillomatosis (Combrinck et al. 2012, Godinez et al. 2013, Sichero et al. 2021); for the differential prevalence of HPV16 variants in anogenital cancers as a function of the anatomical location (Nicolás-Párraga et al. 2016); or for the differential prevalence of HPV16 variants in squamous and in adenocarcinomas (Nicolás-Párraga et al. 2017, Clifford et al. 2019).

The unexpected description of HPV42 as an oncogenic virus

Historical efforts to identify viruses as etiological drivers of cancers had typically focused on detecting targeted suspects through a guided search of genetic material, as in *e.g.* (zur Hausen et al. 1974a, b, Wolf et al. 1975). However, high throughput sequencing techniques applied to cancer samples in clinical settings have provided a plethora of off-target, metagenomic sequences that can potentially contain traces of viral genetic material present in cancer tissue. Starting from an agnostic search for viral sequences in cancer cases, the PV and pathology communities have generated in a very short period of time a sound corpus of knowledge that suggests an etiological role of HPV42 in digital papillary adenocarcinoma (DPA), a rare tumour of the sweat glands. This involvement was first proposed by Vanderbilt et al. (2022b) based on a

systematic survey of shotgun sequencing data aiming at unveiling unknown virus–cancer associations. These authors searched for the presence of viral DNA in almost 60 000 tumour samples, reporting novel potential associations, especially between human herpes virus 6 and neuroblastoma, between human herpes virus 7 and esophagogastric cancer, and, of especial interest for the HPV community, between HPV42 and DPA, based on four DPA cases (Vanderbilt et al. 2022b). Later, this same group confirmed the findings with the detection of HPV42 by *in situ* hybridization in 10 DPA cases and its absence in 20 cases of other adnexal tumours (Vanderbilt et al. 2022a). Independently, Leindecker et al. (2023) provided strong evidence about the presence of HPV42 DNA and RNA in 45 out of a large series of 47 DPA cases, as well as about the possible mechanisms underlying cellular transformation. Only few months after the first descriptions, a number of confirmation studies have further underpinned the role of HPV42 in DPA, in large scale surveys of DPA cases in acral (Kervarrec et al. 2023b) and in nonacral sites (Kervarrec et al. 2023a), as well as in individual case reports (Cascardo et al. 2023). The specificity of the HPV42-DPA association is remarkable because: (i) the acral anatomical location *per se* is not related to a high prevalence or aggressivity of HPV42, as a communication about digital squamous cell carcinomas reports a notable association with different HPVs, chiefly HPV33, but not with HPV42 (Gormley et al. 2011); and (ii) HPV42 is not detected in other cancers ontogenically and/or phenotypically related to DPA, such as hidradenomas or hidradenocarcinomas (Vanderbilt et al. 2022a, Kervarrec et al. 2023b).

HPV42 had never been identified as a possible/probable oncogenic agent for humans. HPV42 and HPV32 are the only known members of AlphaPV-species-1. HPV42 was isolated (Beaudenon et al. 1987a) and characterized (Philipp et al. 1992) from flat vulvar papillomas, while HPV32 was isolated from a focal epithelial hyperplasia of the oral mucosa (Beaudenon et al. 1987b). Despite their close evolutionary relationship, these two viruses display divergent epidemiological patterns and are associated with largely divergent clinical presentations and natural histories of the infection.

HPV42 is often present in different anatomical locations, without any obvious sign of proliferative lesions. The world prevalence of HPV42 in normal cervical cytology samples amounts to 0.6% (95% CI 0.5%–0.6%), compared with 2.8% (95% CI 2.8%–2.9%) for HPV16, the most prevalent viral genotype in this kind of samples. Very interestingly, the prevalence of HPV42 in normal cytology samples varies largely among geographical regions, being highest in Africa [1.2% (95% CI 1.0%–1.5%), compared with 2.4% (95% CI 2.2%–2.6%) for HPV16] and being lowest in Asia [0.3% (95% CI 0.2%–0.3%), compared with 2.3% (95% CI 2.2%–2.4%) for HPV16] (HPV Information Centre). Substantially higher HPV42 prevalence values have been reported in particular populations and anatomical locations, reaching 8% in cervical screening in Ghana (Donkoh et al. 2022), 17.6% in cervical self-sampling in Malagasy women (Vassilakos et al. 2016), or 15% in anal samples of men having sex with men and living with HIV (Damay et al. 2010). Further, HPV42 is the fourth most prevalent HPV found in the semen from infertile men, reaching 8.8% prevalence, with HPV16 being the most frequent type, reaching 22% prevalence (Boeri et al. 2019). Finally, HPV42 has been reported to be very often present in oral samples in a Polish population, with a high oro-genital concordance in the same individual, as well as with a good correspondence of positivity status within couples (Kiwerska et al. 2019).

The HPV42 prevalence in anogenital cancers is low and varies depending on the anatomical location, reaching 0.2% (95% CI 0.2%–0.3%) for cervical cancers, 0.2% (95% CI 0.0%–1.1%) for anal cancers, or 0.1% (95% CI 0.0%–0.6%) for penile cancers (HPV Information Centre). The true contribution of HPV42 to anogenital cancers may actually be lower, after having accounted for the detection of multiple viral genotypes in cancers (Pimenoff et al. 2019). In a series of over 15 000 HPV-positive anogenital cancers, only three cases (one cervical, one vulvar, and one penile lesion, all of them squamous cell carcinomas) contained HPV42 as sole viral genotype and possible etiological agent (Guimera et al. 2013). Other HPV42-related squamous lesions have been described, such as a case of vulvar intraepithelial neoplasia and intravulvar condyloma acuminata (Kacerovská et al. 2014), a case of anal dysplasia (Kreuter et al. 2018) and a case of squamous cell carcinoma in a nonanogenital location (Da et al. 2018). HPV42 has also been sporadically associated to particular proliferative lesions, such as a periungual bowenoid papulosis (Gómez Vázquez and Navarra Amayuelas 2013), but also to seborrheic keratosis-like lesions of the cervix and the vagina (Hennell et al. 2012, Talia and McCluggage 2017, Pujari et al. 2021), as well as in seborrheic keratosis-like lesions of the cervix with high-grade dysplasia (Talia et al. 2022).

Evolutionary correlates of differential oncogenicity among human AlphaPVs

The case for the oncogenicity of HPV42 in DPA offers an opportunity to challenge and update our classical view of HPV-related carcinogenesis. An evolutionary analysis suggests that the oncogenic potential for HPVs is not biunivocally associated to any single evolutionary event or genetic trait. AlphaPVs are the sister group to DyoomikronPVs, isolated from cervicovaginal samples from squirrel monkeys (Chen et al. 2018). The evolutionary relationships among AlphaPV species differ depending on the region of the genome being considered, so that regarding the early ORFs all possibly/probably oncogenic AlphaHPVs are closely related, while regarding the late ORFs (notably the *l1* ORF, used for taxonomy assignments) they are only distantly related and appear dispersed among nononcogenic HPVs (Bravo and Alonso 2004, Garcia-Vallve et al. 2005, Angulo and Carvajal-Rodriguez 2007, Gottschling et al. 2011). When using a genomic approach, AlphaPVs have diverged into four evolutionary clades, all of them spanning viruses that infect catarrhines, from hominoids, (*e.g.* humans and chimpanzees) to cercopithecoids (*e.g.* macaques, colobuses, or baboons) (Fig. 1). There is a rough correspondence between the large, four basal AlphaPV clades and the main clinical manifestations of their infections in humans, roughly skin warts, genital warts, and anogenital lesions (Bravo and Alonso 2004, Schiffman et al. 2005, Bravo and Felez-Sanchez 2015). At this genomic level, the strongest evolutionary signal clusters all possibly/probably oncogenic HPVs into a monophyletic group together with PVs infecting cercopithecoids, all of them often associated to anogenital infections, but not all of them identified as oncogenic in their respective hosts (Kloster et al. 1988, Ostrow et al. 1993, Bravo and Alonso 2004, Chen et al. 2009, 2019, Gottschling et al. 2011, Bergin et al. 2013, Long et al. 2022).

There are few genomic differences among the four AlphaPV clades. The first one is the presence in the genome of AlphaPVs of a nucleotide stretch between the *e2* and the *l2* ORFs, and the nature of the ORFs therein encoded. At the level of the *Papillomaviridae* family, there are four main lineages that present a long DNA segment between the early and the late gene expression cassettes (Garcia-Vallve et al. 2005), and these four segments are not evolutionary related (Willemsen et al. 2019). Unfortunately,

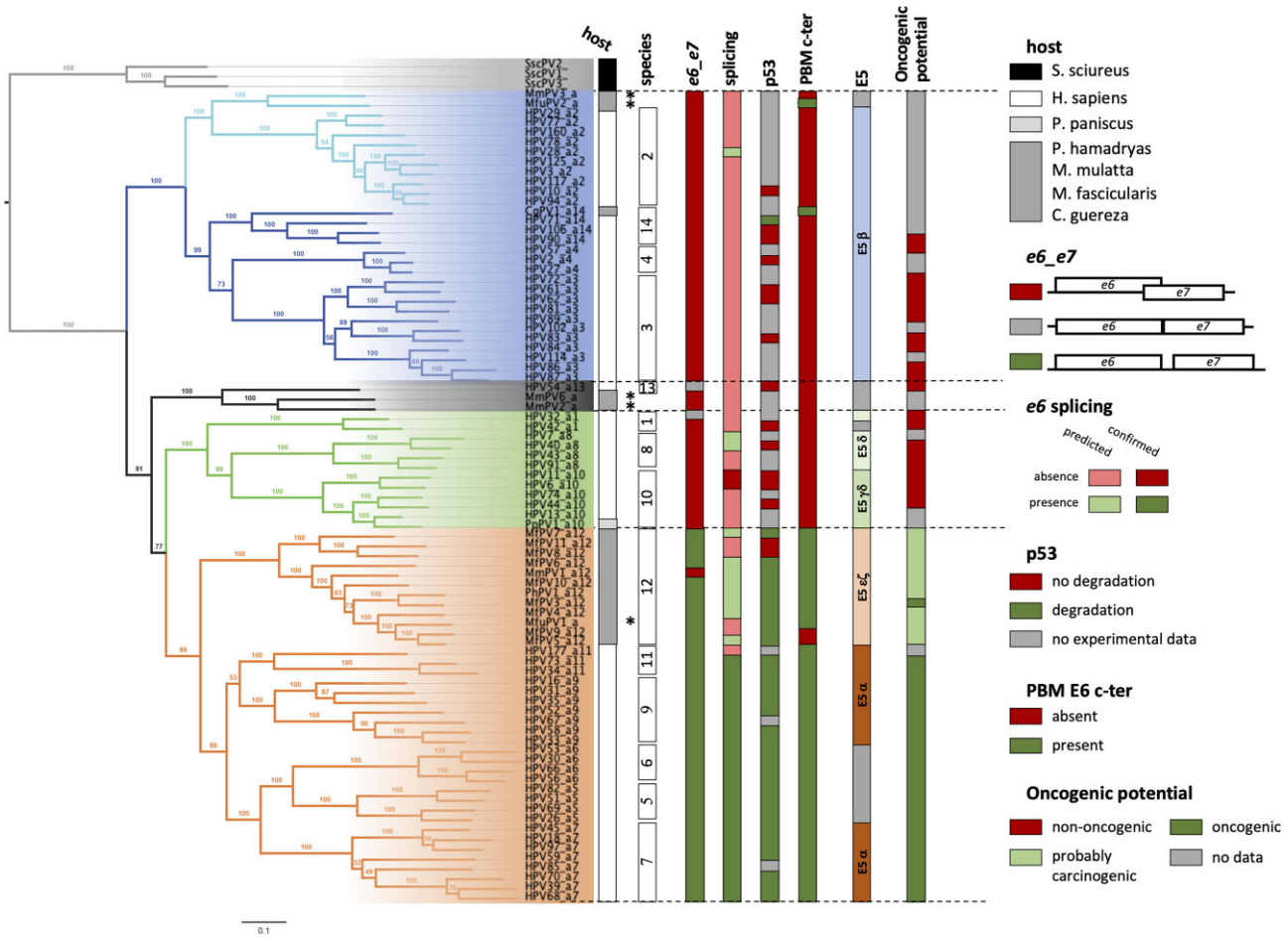

Figure 1. Phylogeny, genomic, and phenotypic traits of Alpha- and DyoomikronPVs. Phylogenetic relationships inferred using maximum likelihood (RAxML) based on the concatenated *e1e2l2l1* ORFs. Numbers in the branches present support after 5000 bootstrap cycles. The tree is rooted using DyoomikronPVs as outgroup. The four main clades within AlphaPVs are identified in blue, grey, green, and orange. Scalebar presents number of substitutions per site. SPECIES: taxonomy species for AlphaPVs. Genotypes labelled by an asterisk are not classified yet. HOST: taxonomy of the host for each genotype. E6_E7: organization of the *e6e7* ORFs; red, *e7* start precedes *e6* stop with a range of 3–39 nucleotides; grey, means *e7* start and *e6* stop are merged in a TAATG sequence; and green, *e6* stop precedes *e7* start with a range of 2–17 nucleotides. SPLICING: presence (green) or absence (red) of a splicing event in the *e6* ORF either predicted (light colour) (Van Doorslaer et al. 2017) or experimentally confirmed (dark colour) (Cornelissen et al. 1990, Nakagawa et al. 2000, Sotlar et al. 2004, Halec et al. 2013). P53: empirical evidence of E6 protein ability to induce degradation of p53 (Fu et al. 2010, Mesplède et al. 2012, Long et al. 2022). PBM: presence (green) or absence (red) of a C-terminal PDZ binding Motif (PBM) in the E6 protein. E5: type of E5 ORF found in each AlphaPV species (Bravo and Alonso 2004). ONCOGENIC POTENTIAL: IARC/ICO classification for HPVs (HPV Information Centre), and literature data for AlphaPVs-species-12 (Kloster et al. 1988, Ostrow et al. 1993, Chen et al. 2009, 2019, Bergin et al. 2013, Long et al. 2022).

all ORFs encoded in this inter_*e2_l2* region have historically been named as *e5*, even if they do not share a common ancestor, which can generate confusion when trying to identify common mechanisms between the cellular effects of unrelated proteins bearing the same name (*e.g.* BPV1_E5 and HPV16_E5 (Dimaio and Petti 2013)). Conversely, evolutionary analyses support monophyly for the inter_*e2_l2* region in AlphaPVs at the DNA level, but not at the protein level (Willemsen et al. 2019). This means that a single event resulted in the emergence of this *ca.* 400 bp inter_*e2_l2* DNA fragment in AlphaPVs, but that the different E5 proteins therein encoded probably have an independent origin (Fig. 2). Indeed, the phylogeny and the chemistry of the E5 proteins in AlphaHPVs suggests multiple origins and divergent functionality, and match well the clinical presentations of the infection (Bravo and Alonso 2004), with E5_alpha being encoded in the genome of (possibly/probably) oncogenic AlphaHPVs, E5_beta being encoded in AlphaHPVs associated to skin warts (*e.g.* HPV2 or HPV3), and E5_gamma and E5_delta being encoded in AlphaHPVs associated to genital warts (*e.g.* HPV6).

The individual histories of evolution and conservation of the ORF encoded in the inter_*e2_l2* region of oncogenic AlphaPVs highlight the connection between evolution and oncogenicity (Bravo and Alonso 2004, Van Doorslaer et al. 2017, Willemsen et al. 2019). Members of the AlphaPVs-species-12 are potentially oncogenic for their cercopithecinae host species (Wood et al. 2004, 2007, Chen et al. 2009, Bergin et al. 2013), and encode for two proteins in tandem, E5_epsilon and E5_dseta, which are distinct in chemistry and sequence from the E5_alpha encoded by the sister taxa of possibly/probably oncogenic HPVs. Further, AlphaPVs-species-5 and species-6 (respectively represented by HPV26 and HPV30; Delius and Hofmann 1994), display a conserved but pseudogenized *e5_alpha* ORF that lacks a starting ATG codon (Fig. S1), and precisely these two AlphaPV-species are associated to a lower oncogenic potential than other probably/possibly oncogenic HPVs. We confirm thus that the nature of the E5 protein encoded in the inter_*e2_l2* segment of AlphaPVs displays a strong correspondence with the clinical presentation and with the oncogenic potential of the corresponding viruses (Fig. 1). This

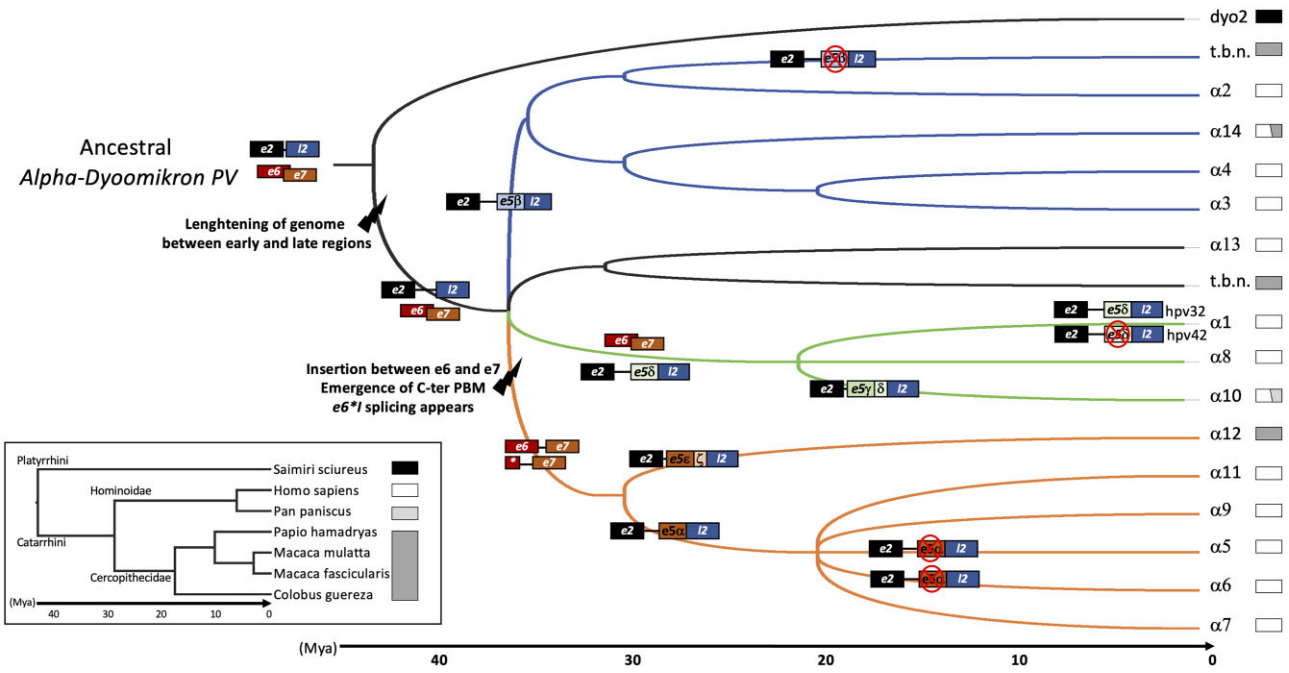

Figure 2. Global scenario of AlphaPV evolution. Cartoon depicting the evolutionary relationships among the four large clades of AlphaPV species, with branches in blue, black, green, and orange. DyoomikronPVs are used as an outgroup. Branches comprising viruses not classified yet are labelled as t.b.n. (to be assigned). Blue and black boxes indicate the genomic organization of the *e2l2* interface between early and late ORF cassettes, as well as the type of E5 protein encoded, if applicable. Red and orange boxes indicate the organization of the *e6* and *e7* ORFs, overlapping or not. The inset presents the evolutionary history of the host species, with the scale in millions of years before present. For each viral branch, coloured box matches the code for the corresponding host species. A time scale is included as a suggestion for the timing of the different evolutionary events in the history of AlphaPVs, assuming a large cophylogeny between viruses and hosts. The genome of the Alpha-DyoomikronPV ancestor, predating the split between Platyrrhini and Catarrhini, did not contain any region between early and late ORF casettes, and the *e6* and *e7* ORFs overlapped. In the genome of the AlphaPV ancestor, an integration event introduced a sequence between the early and the late gene cassettes. This individual event is possibly linked to the basal radiation in AlphaPVs that generated the extant four main clades, all of them spanning PVs infecting hosts in the Hominoidae and in the Cercopithecoidae primate families. Different types of E5 ORFs emerged separately in each of these large clades, and eventually disappeared in specific taxa, such as E5delta in HPV42, or were recently pseudogenized, such as E5_alpha in AlphaPVs species 5 and 6. In the genome of the ancestor of AlphaPVs species 5, 6, 7, 9, 11, and 12, an insertion occurred between the *e6* and *e7* ORFs, possibly linked to the emergence of the C-terminal PDZ binding Motif in the E6 protein, to the gain of function of E6 to induce degradation of p53 and to the appearance of the splicing event in the *e6* ORF. This viral clade, labelled in orange, contains all (probably|possibly) oncogenic HPVs, classified after their oncogenic risk for anogenital and oropharyngeal cancers. HPV42 causative agent of DPA, a rare tumour of the sweat glands, is a member of AlphaPVs-species 1.

connection between epidemiology and evolution for E5 proteins (Bravo and Alonso 2004, Schiffman et al. 2005) contrasts with the relatively little, indirect evidence of translation of the E5 ORFs, as they are located in the 3′-end of the early viral transcripts (Dimaio and Petti 2013, Trammel et al. 2024), as well as with the virtual absence of functional studies focusing on E5 proteins other than E5_alpha (Cartin and Alonso 2003).

The second main qualitative difference between oncogenic and nononcogenic AlphaPVs are the transcription patterns of the *e6* and *e7* ORFs. In oncogenic AlphaHPVs the *e6_e7* expression cassette is transcribed from a single transcription start site, and generates a bicistronic mRNA that can be spliced in the *e6* ORF to encode for a shorter E6*I protein (Schneider-Gädicke and Schwarz 1986, Smotkin and Wettstein 1986, Inagaki et al. 1988). Even if the precise splice donor and acceptor sites are not strictly conserved among closely related viruses, the fact of producing alternative mRNAs by splicing of the *e6* ORF is a signature shared by all oncogenic AlphaHPVs (Cornelissen et al. 1990, Nakagawa et al. 2000, Sotlar et al. 2004, Halec et al. 2013) (Fig. 1). In contrast, nononcogenic AlphaHPVs present a second transcription start site located within the *e6* ORF, that allows for the expression of two different mRNA molecules, a bicistronic mRNA that can conceptually encodes for E6 and E7, and a second one that encodes only for E7 (Inagaki et al. 1988, Smotkin et al. 1989). Further, the *e6* and *e7* ORFs in the bicistronic *e6_e7* mRNAs do not overlap in oncogenic AlphaHPVs while they do overlap in nononcogenic HPVs, so that in the latter the *e6* stop codon is located downstream the *e7* AUG codon (Auslander et al. 2019). The common knowledge in the PV field is that the E7 protein is essentially translated from the *e6*I_e7* mRNA in oncogenic HPVs, and from the *e7* mRNA in nononcogenic HPVs (Schwartz 2013). However, viruses have evolved a plethora of mechanisms that hijack the eukaryotic ribosome for noncanonical translation (Sorokin et al. 2021). Translation of both E6 and E7 could be conceived from the *e6_e7* bicistronic mRNA by means of leaky scanning in both oncogenic and nononcogenic AlphaHPVs (Stacey et al. 2000), and/or by means of reinitiation upon termination in oncogenic AlphaHPVs only. The lack of overlap between the *e6* and *e7* ORFs is an evolutionary novelty of the monophyletic group of oncogenic primate AlphaPVs (Tang et al. 2006) (Fig. 2). It can be thus hypothesized that the equilibrium between E6 and E7 levels and the downstream associated effects could be under (post)transcriptional control, through modulation of splicing activity or under translational control, through modulation of noncanonical translation events. Such differences in the E6:E7 ratio could thus vary as a function of the cell type, cell differentiation stage, cell cycle, or local or systemic immune status, ultimately

modulating the probability of the different infection outcomes. Should this be the case, the combination of the ability of generating *e6∗I_e7* transcripts together with the lack of overlap between *e6* and *e7* could have provided the clade of possibly/probably oncogenic AlphaPVs with an additional mechanism to regulate the E6:E7 ratio, and thus allow novel ways of exploiting the host cell and eventually lead to particular clinical presentations of the infection.

The third main qualitative difference between oncogenic and nononcogenic AlphaHPVs is the ability of the E6 protein in oncogenic HPVs to induce degradation of the cellular protein p53, as described first for HPV16 and HPV18 (Scheffner et al. 1990, Werness et al. 1990), *via* an interaction with the LxxLL motif of the cellular E3 ubiquitin ligase E6-associated protein (E6AP) (Huibregtse et al. 1991, Zanier et al. 2013, Martinez-Zapien et al. 2016). The E6-E6AP interaction is an evolutionary ancient signature shared by members of the Alpha-OmikronPVs, while PVs in other distantly related crown groups such as such as Beta-Xi or Delta-Zeta-PVs display rather an E6-MAML1 interaction (Brimer et al. 2017). In its turn, the ability of this E6-E6AP complex to promote p53 degradation is an evolutionary recent signature, displayed by a well-defined clade of AlphaPVs (Hiller et al. 2006, Fu et al. 2010, Mesplède et al. 2012) that are monophyletic when considering the early genes (Bravo and Alonso 2004). The evolutionary explanation proposed to account for this pattern is that in the most recent common ancestor of AlphaPVs-species-5, 6,7, 9, 11, and 12 the *e6* ORF acquired changes that allowed for the interaction E6-E6AP-p53, ultimately resulting in the degradation of cellular p53 (Bravo and Felez-Sanchez 2015, Willemsen and Bravo 2019) (Fig. 2). Indeed, a virus–host codivergence pattern has been experimentally demonstrated for species-specific interactions between E6 and p53 (Long et al. 2022), and a fraction of the differences in oncogenic potential among oncogenic HPVs may actually be related to small differences in the E6-E6AP-p53 interaction, that eventually modulate the intensity of p53 degradation (Conrady et al. 2020). Beyond p53 degradation, E6 proteins from oncogenic AlphaHPVs display a vast interaction repertoire with cellular proteins mediated by a small PDZ-binding motif present in the E6 C-terminal sequence (Nomine et al. 2003, Thomas et al. 2016, Webb Strickland et al. 2018). Within AlphaPVs, only the E6 proteins of possibly/probably HPVs, i.e. species 5, 6, 7, 9, and 11, display such a PDZ-binding motif in their C-termini (Fig. 1). Closely related E6 sequences show qualitative and quantitative differences in their protein–protein interaction repertoire, associated to minor disparities in the PDZ-binding motif display (Gogl et al. 2022). Many viral proteins display indeed a PDZ-binding motif in their C-termini, and the protein–protein interaction networks provided through this small sequence stretch may be an essential element of the viral parasitic lifestyle (Davey et al. 2011, Javier and Rice 2011). The strong concordance in oncogenic HPVs between the lack of overlapping between *e6* and *e7*, possibly related to a small nucleotide insertion (Auslander et al. 2019), and the presence of a PDZ-binding domain, makes it tempting to hypothesize that both traits are related to a single evolutionary event.

A final qualitative difference between the main clades within AlphaPVs are the codon usage preferences of early and late genes (Félez-Sánchez et al. 2015). Among the very few things that all viruses have in common, a fundamental one is that all viruses are parasites of the translation machinery of the infected cell. Codon usage preferences and the associated frequency of CpG and TpA dinucleotides are thus central to the virus–host interplay during gene expression, because they condition the expression ability of a gene (Plotkin and Kudla 2011, Brule and Grayhack 2017, Callens et al. 2021) and also because they modulate the immune response against the viral genes (Li et al. 2012, Mordstein et al. 2020). Indeed, codon recoding strongly modifies expression of viral genes (Burns et al. 2006, Lauring et al. 2012), to the extent that a full novel generation of vaccines, including RNA-based ones, applies synonymous recoding (Martínez et al. 2016, Zhang et al. 2023). Papillomaviruses genomes are A + T rich and their codon usage preferences differ from the average ones of their hosts (Zhao et al. 2003, Bravo and Müller 2005). However, different tissues express different repertoires of tRNAs and codon usage preferences may be tissue-dependent (Dittmar et al. 2006, Kames et al. 2020, Akins et al. 2023), and it has been proposed that viruses display different codon usage preferences depending on the tissues they infect (Hernandez-Alias et al. 2021). In the case of PVs, codon usage preferences of capsid genes are limited by the tRNA availability in the upper skin layers (Zhou et al. 1999, Gu et al. 2004, Zhao et al. 2005). These findings are consistent with the changes in viral gene expression changes across the differentiation stages of the infected keratinocyte. Further, codon usage preferences largely differ between AlphaHPVs and Beta- and GammaHPVs (Cladel et al. 2010, Félez-Sánchez et al. 2015), suggesting that viral life style strongly conditions codon usage in viruses that infect the same human host. Finally, for AlphaHPVs, codon usage patterns cluster together viruses in three large groups, corresponding to evolutionary close viruses associated to similar natural histories of the infection (Félez-Sánchez et al. 2015), corresponding to a differential match to the average human codon usage preferences (Fig. 3) (Bourret et al. 2019). Thus, oncogenic HPVs display codon usage preferences qualitatively distinct from those of other AlphaHPVs, albeit no quantitative differences can be established among oncogenic HPVs connecting codon usage preferences and differential oncogenicity.

Why HPV16? Why, now HPV42?

After several decades of research about the oncogenicity of certain HPVs, nothing of what we knew about HPV42 let us think that it could be related to any cancer. The intellectual challenge is thus to reconcile the experimental evidence strongly supporting an etiological role of HPV42 infections in DPA, a rare cancer of sweat glands, with the absence of any of the classical signatures of oncogenic HPVs in the genome of HPV42: (i) it lacks an ORF in the inter_*e2*_*l2*, region and does not display an eroded coding signal, while the closely related HPV32 encodes for an E5_delta protein; (ii) the *e6*_*e7* expression cassette corresponds to a nononcogenic pattern, the *e7* AUG start codon being located 25 nucleotides upstream the *e6* UAA stop codon; (iii) no splicing signals for *e6∗Ie7* transcripts are predicted (Van Doorslaer et al. 2017), and no spliced transcripts have been detected (Leiendecker et al. 2023); (iv) HPV42_E6 can bind human E6AP (Leiendecker et al. 2023), but the expression of HPV42_E6 in human cells does not induce degradation of p53 (Fu et al. 2010, Mesplède et al. 2012, Leiendecker et al. 2023); finally, (v) HPV42_E6 lacks the terminal PDZ-binding domain present in the C-terminus of E6 proteins in oncogenic HPVs. The only element that could point to a carcinogenic potential for HPV42 is that HPV42_E7 presents an aspartate residue upstream the LxCxE motif (Guimera et al. 2013), which enhances E7-pRb binding (Heck et al. 1992), and indeed, experimental data show that overexpression of HPV42_E7 results in cellular transformation and *in vivo* tumour growth (Leiendecker et al. 2023).

We propose here that a perspective of the virus–host interactions centred on cell phenotypes could help understand the

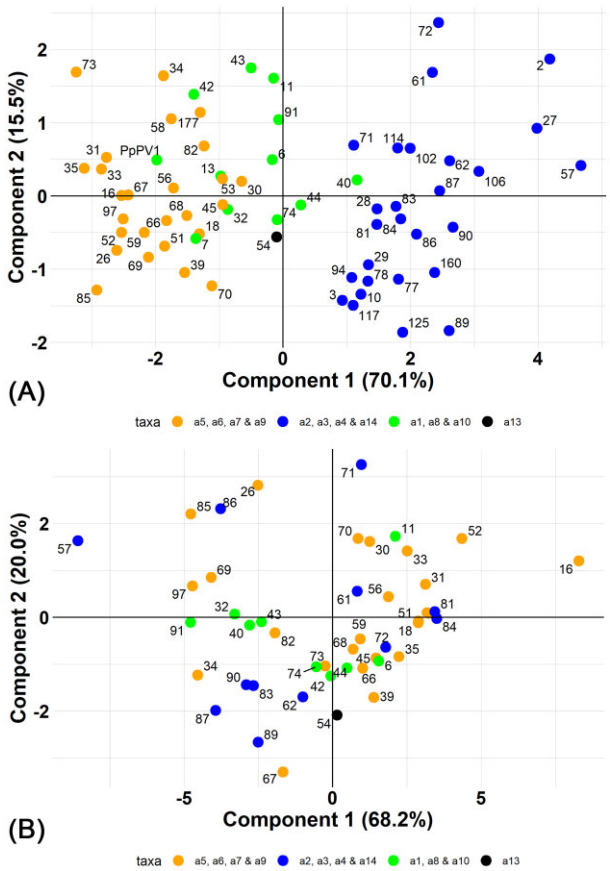

Figure 3. Clustering of AlphaPVs after epidemiological characteristics and codon usage preferences. Principal component analyses for epidemiological variables (A) and for codon usage preferences (B) of AlphaHPVs. Values in the axes reflect the percentage of the total variance captured by the corresponding component. Viral species are stratified into the main four evolutionary clades. Numbers correspond to the HPV genotype. Epidemiological variables used: genotype-specific prevalence in asymptomatic cervical samples and in cervical, vaginal, vulvar, anal and penile cancers (HPV Information Centre), genotype-specific median duration of the cervical infection (Goodman et al. 2008, Trottier et al. 2008, Schmeink et al. 2013, Ramanakumar et al. 2016), and genotype-specific 1-year and 5-years cumulative first detections of cervical infection (Malagón et al. 2023). Codon usage was evaluated using the codon usage similarity index (COUSIN) for each of the *e6*, *e7*, *e1*, *e2*, *l2*, and *l1* ORFs against the average human codon usage preferences (Bourret et al. 2019).

riddle of rare clinical and phenotypic presentations associated to common, largely asymptomatic viral infections. Under this perspective, the differential probabilities for the repertoire of natural histories of the infection depend on the particular interaction of a specific viral genotype with a specific cell phenotype. This model does not stem from incomplete knowledge, but integrates instead the inherent nondeterminism of biological processes, where gene expression and cellular states fluctuate unpredictably (Raser and O'Shea 2005), including a multitude of 'non canonical', poorly understood mechanisms that are most likely related to biological noise (Pickrell et al. 2010, Sibley et al. 2016, Liu et al. 2019, Yu and Kim 2020, Sorokin et al. 2021, Porter 2023). Our common understanding of viral infections partly integrates a static perspective in this regard, when referring to viral tropism or to infection-permissive cells or opportunistic infections. But we want to stress here that the cellular phenotype that is relevant for viral infections is a dynamic one: it can be stable, (*e.g.* a definite cell type, a particular epigenetic state) or transient, (*e.g.* a stage along a cell differentiation process, or over cell cycle, or a transient epigenetic state); it may depend on the context and vary across space (*e.g.* for similar cell types in different tissues or organs), or across time (*e.g.* with life history traits such as puberty, menstruation, reproduction, menopause, or senescence); and it can further depend on the immune status of the individual (*e.g.* local or systemic immunodepression of idiopathic origin, or linked to infections such as HIV, or associated to medical treatments).

We understand here cellular phenotypes as a quasi-discontinuous repertoire of states available to a given cell, that are connected by probabilities of transition from one to another. Such transitions can be stochastic, or favoured by intrinsic or extrinsic factors. A particular cellular state leads to particular replication, transcription and translation viral patterns, allowing for different infection profiles, even at the very fine scale of cellular cycling timing (Schulte and Andino 2014, Petkidis et al. 2024). This cellular context will be modified by infection itself, so that the actual phenotype of the infected virocell (Forterre 2011), and thus the individual outcome of the infection, may be subject to complex feedback cycles. This approach for interpreting the diversity of natural histories associated to a parasite–host interaction becomes especially useful when applied to resident members of the microbiota.

Small DNA viruses, notably PVs and PyVs, are fundamental components of the healthy human microbiota (Foulongne et al. 2012, Ma et al. 2014, Rascovan et al. 2016). The prevalence of each individual viral genotype varies among individuals, but also differs among anatomical sites and changes over lifetime (de Koning et al. 2007, Hannigan et al. 2015, Amorrortu et al. 2022). As it is the case for most individual PV and PyVs genotypes, HPV42 is part and parcel of this healthy skin human microbiota (Ma et al. 2014) but most HPV42 infections are not associated to any clinical sign. In our perspective of interpreting the outcomes of the infection under the light of specific virus genotype–cell phenotype interactions, we propose that the vast majority of HPV42 infections on the human skin are asymptomatic, but that in rare occasions HPV42 may gain access to a rare cell (pheno)type present in the sweat glands, with an increased probability of resulting in transformation and cancer. Specific cells in skin appendages have actually been proposed to be '*infection reservoirs*' for certain HPVs, mostly specific cells in hair follicles (Schmitt et al. 1996, Boxman et al. 1997) but also in sweat glands (Egawa 2005). The skin is indeed a highly heterogeneous, complex cellular environment that we start only to be able to engineer and reproduce (Lee et al. 2020). The variety of skin cell (pheno)types allows for a large variety of virus–host interactions, as the precise viral transcription and translation patterns will depend on the biochemical and cellular contexts provided by the individual infected cell, (Butz and Hoppe Seyler 1993, Cid et al. 1993, Schmitt et al. 1996, Schenkel et al. 1999). This overall perspective on cellular phenotypes can provide a general framework for the hit-and-run mechanism invoked for the long-lasting puzzle of the role of BetaHPVs infections in nonmelanoma skin cancer (Rollison et al. 2019), reconciling this view with the conflicting proposal of a cancer-protective role of cutaneous PV infections as modulators of the T-cell immunity (Strickley et al. 2019), and helping to frame the interesting scientific controversy it has generated (Lambert et al. 2020, Strickley et al. 2020). Recent transcriptomic data confirm this view, with specific viral transcripts being detected in specific cellular subpopulations across the keratinocyte differentiation gradient (Bedard et al. 2023), as well as recent proteomic data providing evidence of spatial

translation heterogeneity in cutaneous HPVs infections (Schäfer et al. 2023).

By focusing on the interaction between viral genotypes and the transient, context-dependent nature of cell phenotypes, we will gain a deeper understanding of the how common asymptomatic infections may be related to rare cancers like DPA.

How a virus genotype–cell phenotype perspective can help guide our understanding of the diversity of natural histories of the infection

Traditional pathogen–host paradigms, such as the Koch–Pasteur model, rely on a *one-to-one* connection (or a simplified version of it) between pathogen and disease. But this paradigm does not help account for the diversity of natural histories of viral infections, particularly those from common microbiota members. In many cases we observe one virus causing a large spectrum of clinical presentations of the infection (*one-to-many*), or distinct viruses causing the same disease (*many-to-one*). A cell phenotype-centred perspective provides a probabilistic framework to understand these diverse relationships, and it generates key questions that will need to be answered in order to properly understand the underlying causal mechanisms.

One-to-one relationships: HPV42 and DPA

In the case of HPV42 and DPA the evolutionary question is, given the close relationship between HPV32 and HPV42, why there are no HPV32-driven DPAs?; from the ontogeny standpoint, are HPV32 and/or HPV42 associated to malignant proliferations of cell (pheno)types close to those associated to DPA? In analogy, the causative role of Merkel cell polyomavirus in a substantial fraction of Merkel cell carcinomas (Feng et al. 2008), raises the question of whether the closely related *Pan troglodytes verus* polyomavirus 2a and *Gorilla gorilla gorilla* polyomavirus 1 (Polyomaviridae Study Group of the International Committee on Taxonomy of Viruses et al. 2016) might be involved in malignant proliferations analogous to Merkel cell carcinomas in their respective host species.

One-to-many relationships

(i) The extreme oncogenicity of HPV16. Possibly, the most enduring puzzle after 50 years of research on HPVs and cancers is not how certain HPVs cause certain cancers, but why HPV16 is uniquely oncogenic compared to its close relatives, *e.g.* HPV31 and HPV35. Indeed, HPV16 is an outlier compared to any other AlphaHPV in terms of epidemiology of anogenital asymptomatic infections, considering incidence, prevalence, and duration of asymptomatic infections, but also regarding the individual contribution to HPV-driven cancers (Fig. 3) (Goodman et al. 2008, Trottier et al. 2008, Schmeink et al. 2013, Ramanakumar et al. 2016, Malagón et al. 2023, HPV Information Centre). Genomic and functional hallmarks allow to pinpoint (possibly/probably) oncogenic HPVs from other AlphaHPVs (Bravo and Alonso 2004, Schiffman et al. 2005), but they do not serve to establish qualitative nor quantitative differences in oncogenic potential among them, as noted previously (Hiller et al. 2006, Muench et al. 2009). The viral genotype–cell phenotype perspective suggests to focus on specific cell precursors related to particular anogenital transformations, as it has been shown that a discrete population of cells in the cervical transition zone is enriched in HPVs-driven cervical cancer (Herfs et al. 2012). Analogous specific keratinocyte precursors are more prone to develop cutaneous squamous cell carcinomas upon MmuPV1 infection (Moreno et al. 2022). It could thus be hypothesized that the higher relative contribution of HPV16 to anal or to oropharyngeal cancers compared to cervical cancers could be related to the differential frequency of a particular cell phenotype in these anatomical locations. Identifying such particular cell phenotypes would be of interest because the microanatomy differs between cervical and anal squamocolumnar junctions (Yang et al. 2015), but also because we still lack a proper understanding of the natural history of HPV-driven oropharyngeal cancers in terms of precursor lesions and progression pace and stages (Roberts et al. 2019).

(ii) HPV18 and adenocarcinomas. The relative contribution of HPV18 is substantially higher in adenocarcinomas compared to squamous cell carcinomas (Reynders et al. 2023), which could point towards a particular interaction between AlphaPVs-species-7 and certain mucosal-related cell phenotypes.

(iii) HPV33 and multiphenotypic sinonasal carcinomas. HPV-related multiphenotypic sinonasal carcinomas present features of adenoid cystic carcinomas (Bishop et al. 2013) and are most often associated to HPV33 and other AlphaHPVs-species-9, with only a minor contribution of HPV16 to this specific disease (Bishop et al. 2017). HPV-related multiphenotypic sinonasal carcinomas share typical diagnostic features with other HPV-driven cancers, such as p16 overexpression (Bishop et al. 2017). Given the substantial albeit low contribution of HPV33 to anogenital cancers (10–20 times lower than that of HPV16) and given that little qualitative differences have been pinpointed so far at the mechanistic level between HPV16 and HPV33 (Muench et al. 2009, Thomas et al. 2016, Gogl et al. 2022), we interpret that the oncogenic potential of closely related HPVs may sharply differ depending on the specific phenotype of the infected cell.

Many-to-one relationships

Multifocal epithelial hyperplasia is a benign proliferative condition of the oral mucosa (Estrada 1956, Archard et al. 1965) that presents increased prevalence in small human populations, mostly of American-native ancestry, although cases have been reported in individuals of very different genetic background (Sethi et al. 2022). This disease exemplifies a many-to-one relationship, as it is associated to infections by two distant genotypes, HPV13 and HPV32, (Henke et al. 1987, 1989, Beaudenon et al. 1987b). The sole case-control study available confirms HPV13 as causative agent in children of the Embera–Chami community in Colombia (Cuberos et al. 2006). A clinical presentation similar to focal epithelial hyperplasia has been communicated in chimpanzees, reaching high prevalence in a small zoo community, 15 out of 44 animals showing symptoms (Hollander and Van Noord 1972). The viral causative agents of focal epithelial hyperplasia in bonobos and in chimpanzees are close relatives of HPV13 (Van Ranst et al. 1991, Scinicariello et al. 1997), all of them belonging together in a monophyletic clade within AlphaPVs-species-10. The epidemiological and evolutionary relationships among these viruses raise the question of whether a specific oral mucosal cell phenotype is present in the oral mucosa of primates that, when subject to

viral-induced benign proliferation, results in the clinical phenotype of focal epithelial hyperplasia, independently of the precise genotype of the virus that triggered the disease. Indeed, viruses closely related to HPV13, such as HPV44 or HPV74, members of the same species, have not been reported in focal epithelial hyperplasia, and the same holds true for HPV42, close relative of HPV32. To further complicate the picture, PV-driven focal epithelial hyperplasia has also been reported in brown howler monkeys (Pulecio-Santos et al. 2024), and the associated PV belongs into DyoomikronPVs, the sister group of AlphaPVs (Silvestre et al. 2016). Thus, on the one hand three closely related viruses are associated to a same, distinct clinical presentation of the infection in sister host species, which is useful as it provides a good yardstick for dating PV evolution (Willemsen and Bravo 2019), but on the other hand the same clinical presentation in humans is associated to two genetically very distant HPVs, while the respectively closely related HPVs are not. Finally, a distantly related virus is associated to a similar disease in a distantly related host species. The mechanisms for which these PVs induce proliferation in this putative cell phenotype would not necessarily need to be similar, if the clinical presentation is mostly determined by the proliferating cell phenotype, which would allow for the large genetic gap between the etiological agents of the disease. The key determinant of the clinical presentation of the infection would thus be the cell phenotype and not the viral genotype itself.

Focusing on viral genotype–cell phenotype interactions may thus provide a unifying framework to understand the repertoire of natural histories of the infection. Identifying the specific cellular phenotypes involved in proliferative diseases could help explain why certain viruses are more or less prone to cause cancers in certain anatomical locations and under certain conditions, while closely related viruses do not. This perspective allows to integrate long-lasting genetic and environmental factors with more fluid and transient cellular states, acknowledging the role of stochasticity and biological noise as a central factor at determining the outcome of viral infections.

Corollary

Every surface in our bodies is a small universe, homeplace to milliards of viruses, bacteria, and fungi. DNA viruses, particularly small DNA viruses, are central components of the human skin virome. The vast majority of infections by HPVs and by human PyVs are asymptomatic, but a few, evolutionary close HPVs cause both benign and malignant proliferative diseases. Given the high prevalence of PVs asymptomatic infections in the human population, symptomatic infections, and especially cancers, play a minimal role in the population and evolutionary dynamics of these viruses. We interpret that the actual eco-evolutionary pressures driving PVs evolution are mostly related to the asymptomatic, commensal-like virus lifestyle as their main strategy to exploit the host. The different clinical manifestations are in most cases unfortunate spill-overs of this commensal-like nature.

HPVs have not evolved 'to cause' or 'because they cause' common cancers, such as cervical cancer, or rare cancers, such as DPA. The oncogenicity of a handful of HPVs may play only a minor role on virus' evolution. We propose that a perspective centred on the differential probabilistic interactions between viral genotypes and host cell phenotypes offers a powerful framework to understand how common viruses can cause rare proliferative diseases.

Host cell phenotypes are inherently dynamic. They can be stable, such as differentiated cell types, but are most often transient, fluctuating over time and space, across developmental and life history changes, across tissues, and hormonal cycles. Cell phenotypes vary also with local and systemic changes in the immune status such as in infection-mediated or iatrogenic immune suppression. Finally, cell phenotypes will vary depending on the interaction with the local microbiota, so that the presence of a given assembly of intracellular or extracellular viruses/bacteria/fungi may modify the cellular phenotype and thus the response to a same individual cell to future microbial challenges.

The main challenge lies in moving beyond the deterministic models of biology focusing on genetic (be they on the side of the pathogen or the host) and environmental factors, towards an understanding that integrates transient, fluid interactions related to probabilistic transitions between different biological states. Most often uncertainty in biology is conceived as lack of knowledge, so that if we could have more data, finer in space and in time, addressing multiple integration levels, we would be able to understand complex biological systems and to predict biological interactions. Unfortunately, this Newtonian-like conception of biology collides with the probabilistic nature of all information transfer processes in biology, with heritable nongenetic heterogeneity, and with the growing evidence about the importance of intrinsic and of extrinsic noise in biology.

We require a conceptual transition towards a conception of biological reality as an ensemble of quasi-discontinuous states, connected by transition probabilities. For common members of the microbiota that can trigger disease under very specific cellular contexts, crucially for HPVs and the cancers they cause, we urgently need to understand the continuum between the normal and the pathological. As Georges Canguilhem suggested, '*the continuity of a transition between one state and another can certainly be compatible with the heterogeneity of these states*' (Canguilhem, Georges 1966). We hope that our proposal to focus on transient cellular phenotypes can contribute to this understanding.

Supplementary data

Supplementary data is available at *FEMSRE Journal* online.

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