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The low-risk papillomaviruses

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ABSTRACT

Human Papillomavirus (HPV) research has been dominated by the study of a subset of Alpha papillomaviruses that together cause almost 5% of human cancers worldwide, with the focus being on the two most prominent of these (HPV16 and 18). These viruses are referred to as 'high-risk' (hrHPV), to distinguish them from the over 200 prevalent HPV types that more commonly cause only benign epithelial lesions. The 'low-risk' (lrHPV) term used to describe this group belies their cumulative morbidity. Persistent laryngeal papillomas, which occur rarely in children and adults, require regular surgical de-bulking to allow breathing. Such infections are not curable, and despite being caused by HPV11 (a lrHPV) are associated with 1–3% risk of cancer progression if not resolved. Similarly, the ubiquitous Beta HPV types, which commonly cause asymptomatic infections at cutaneous sites, can sometimes cause debilitating papillomatosis with associated cancer risk. Recalcitrant genital warts, which affect 1 in 200 young adults in the general population, and even the ubiquitous common warts and verrucas that most of us at some time experience, cannot be reliably eradicated, with treatment strategies advancing little over the last 100 years. The review highlights molecular similarities between high and low-risk HPV types, and focuses on the different pathways that the two groups use to ensure persistent infection and adequate virus shedding from the epithelial surface. Understanding the normal patterns of viral gene expression that underlie lesion formation, and which also prevent loss of the infected basal cells in established lesions, are particularly important when considering new treatment options. Finally, the common requirement for deregulated viral gene expression and genome persistence in development of cancers, unites both high and low-risk HPV types, and when considered alongside viral protein functions, provides us with a working understanding of the mechanisms that underlie HPV-associated pathology.

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1. Background

One of the most distinctive characteristics of the papillomavirus group is their genotype-specific host-restriction, and the preference of particular papillomavirus types for distinct anatomical sites where they cause lesions with distinctive clinical pathologies (Doorbar et al., 2015; Egawa et al., 2015). The association of 'high-risk' HPV (hrHPV) types with cervical cancer is well established, and has provided a rationale for the introduction of HPV DNA testing in cervical screening, as well as the development of prophylactic vaccines against HPV16 and 18, which are the major papillomavirus types responsible for cervical cancer (zur Hausen, 2009). In contrast, 'low-risk' HPV (lrHPV) types, which

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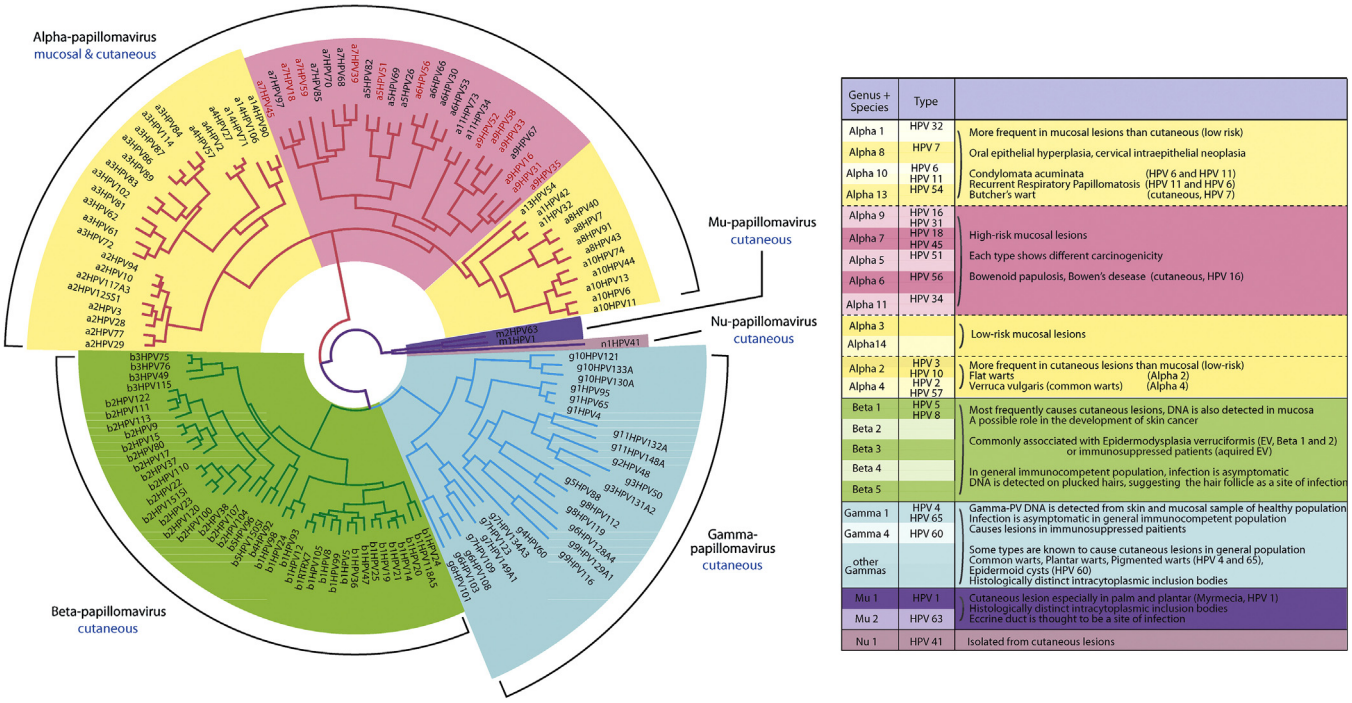

Genus + Species	Type	
Alpha 1	HPV 32	More frequent in mucosal lesions than cutaneous (low risk)
Alpha 8	HPV 7	Oral epithelial hyperplasia, cervical intraepithelial neoplasia
Alpha 10	HPV 6 HPV 11	Condylomata acuminata (HPV 6 and HPV 11) Recurrent Respiratory Papillomatosis (HPV 11 and HPV 6)
Alpha 13	HPV 54	Butcher's wart (cutaneous, HPV 7)
Alpha 9	HPV 16 HPV 31	High-risk mucosal lesions Each type shows different carcinogenicity Bowenoid papulosis, Bowen's desease (cutaneous, HPV 16)
Alpha 7	HPV 18 HPV 45	
Alpha 5	HPV 51	
Alpha 6	HPV 56	
Alpha 11	HPV 34	
Alpha 3		Low-risk mucosal lesions
Alpha14		
Alpha 2	HPV 3 HPV 10	More frequent in cutaneous lesions than mucosal (low-risk) Flat warts (Alpha 2)
Alpha 4	HPV 2 HPV 57	Verruca vulgaris (common warts) (Alpha 4)
Beta 1	HPV 5 HPV 8	Most frequently causes cutaneous lesions, DNA is also detected in mucosa A possible role in the development of skin cancer
Beta 2		Commonly assocciated with Epidermodysplasia verruciformis (EV, Beta 1 and 2) or immunosuppressed patients (aquired EV)
Beta 3		
Beta 4		In general immunocompetent population, infection is asymptomatic DNA is detected on plucked hairs, suggesting the hair follicle as a site of infection
Beta 5		
Gamma 1	HPV 4 HPV 65	Gamma-PV DNA is detected from skin and mucosal sample of healthy population Infection is asymptomatic in general immunocompetent population Causes lesions in immunosuppressed paitients
Gamma 4	HPV 60	
other Gammas		Some types are known to cause cutaneous lesions in general population Common warts, Plantar warts, Pigmented warts (HPV 4 and 65), Epidermoid cysts (HPV 60) Histologically distinct intracytoplasmic inclusion bodies
Mu 1	HPV 1	Cutaneous lesion especially in palm and plantar (Myrmecia, HPV 1) Histologically distinct intracytoplasmic inclusion bodies Eccrine duct is thought to be a site of infection
Mu 2	HPV 63	
Nu 1	HPV 41	Isolated from cutaneous lesions

Fig. 1. Evolutionary Relationship between Human Papillomaviruses. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
(A) The human papillomaviruses types found in humans fall into five genera, with the Alpha-, Beta- (blue) and Gammapapillomavirus (green) representing the largest groups; Human papillomaviruses types from the Alphapapillomavirus genus are often classified as low-risk cutaneous and low-risk mucosal (yellow); or high-risk (pink) according to their association with the development of cancer. The high-risk types highlighted with red text are confirmed as "human carcinogens" on the basis of epidemiological data. The remaining high-risk types are "probable" or "possible" carcinogens. Although the predominant tissue associations of each genus are listed as either cutaneous or mucosal, these designations do not necessarily hold true for every member of the genus. The evolutionary tree is based on alignment of the E1, E2, L1, and L2 genes (Doorbar et al., 2012). HPV sequence data was obtained from PaVE (https://pave.niaid.nih.gov/#home). (B) The tropism and pathogenesis of each HPV species are listed. Tissue tropism has become controversial as a wide range of HPV DNA can be detected at mucosal and cutaneous sites from the general population. In fact, the sites of infection, and whether HPV is present as 'contaminating virus particles or as micro lesions or latent infection is not known yet. Each species tend to show a distinctive tropism when causative association with a lesion is demonstrated. The typical relationships between HPV type and disease are listed.

encompass the majority of the 200 or so known human papillomaviruses, cause benign hyper proliferative lesions, and are not a frequent cause of malignant carcinoma among the general population (Fig. 1). Because of their lower impact as carcinogenic agents (and thus 'lower-risk'), research on lrHPV types has not been prioritized. In general, lesions caused by lrHPVs are self-limiting, and are eventually cleared by the host immune system, which is also the case for the hrHPV types that produce only asymptomatic infection in most individuals. However, among susceptible populations, lrHPV types can be refractory to treatment, and show problematic pathologies, including recurrent respiratory papillomatosis (RRP) and Epidermodysplasia Verruciformis (EV), and in these situations can sometimes be associated with the development of cancers. In this review, we overview the pathogenicity and carcinogenicity of lrHPV in comparison with hrHPV, and aim to emphasize that similar life cycle concepts explain many aspects of their pathogenesis, and some aspect of their infrequent carcinogenesis. As there are already a number of well-written reviews covering different aspect of this topic, our focus is on outline concepts, with the aim of keeping the review concise (Carifi et al., 2015; Doorbar et al., 2015; Egawa et al., 2015; Howley and Pfister, 2015; Quint et al., 2015; Roman and Munger, 2013; Vande Pol and Klingelhutz, 2013).

2. Evolution and the prevalence of HPV-associated asymptomatic infections

With over 240 distinct human and animal papillomavirus types classified into 37 genera, with 5 genera of HPV spread among them (Alpha, Beta, Gamma, Mu and Nu), papillomavirus may perhaps be considered as one of the most successful families of vertebrate viruses (Bernard et al., 2010; de Villiers et al., 2004; Van Doorslaer, 2013) (Fig. 1). Their origin is linked to changes in the epithelium of their ancestral host that occurred at least 350 million years ago. Since then, they have co-evolved with their various host species, paralleling the evolution of host resources or attributes, such as the presence or absence of fur or the evolution of sweat glands (Bravo and Felez-Sanchez, 2015; Van Doorslaer, 2013). They are now found in birds, reptiles, marsupials and mammals. Through this route, papillomaviruses have each developed their distinctive molecular strategies, allowing each of them to complete their life cycle at specific sites of infection (Fu et al., 2010; Tan et al., 2012; Thomas et al., 2016; Van Doorslaer and Burk, 2010), and as a consequence of this, they show remarkable species specificity and a great diversity of epithelial tropisms and clinical pathologies. Unfortunately, our understanding of these adaptations is very limited, as most research has focused on the oncogenic property of viral genes and the process of malignant progression, rather than virus fitness and evolutionary adaptation to a specific epithelial site. It seems in fact that lrHPV types are maintained and propagated in the general population as successfully as the oncogenic high-risk types (de Koning et al., 2015; de Koning et al., 2007, 2010; Desai et al., 2011; Stanley et al., 2012; Weissenborn et al., 2012). Interestingly, the non-productive or abortive hrHPV infections that represent the precursors of HPV-associated cancer are not obviously beneficial from a virus-fitness point of view and the precise reason why