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Review Article

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Recent Developments in the Understanding of Bovine Papillomavirus

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A B S T R A C T

Papillomaviruses are epitheliotropic, non-enveloped, double-stranded DNA viruses. The *Papillomaviridae* family consists of 5 genera affecting cattle, including *Delta papillomavirus*, *Xi papillomavirus*, *Epsilon papillomavirus*, *Dyoxi papillomavirus*, and *Dyokappa papillomavirus*. Among these genera, 24 types of bovine papillomaviruses (BPVs) have been reported to date. The BPV genome is almost 8 Kb in size and is organized into three regions: early (E), late (L), and long codon region (LCR), The E region codes for replication proteins (E1, E2, E4) as well as oncoproteins (E5, E6, and E7). The L1 ORF is the most conserved among PVs and for this reason, it is employed in virus classification. The present PV diversity can be explained by multiple evolutionary mechanisms. Virus host-divergence is an important evolutionary force, however this force solely cannot explain the evolution of PVs and their diversity, thus alternative mechanisms such as within-host virus duplication, recombination, viral sorting, or viral adaptation after a host switch, may therefore contribute considerably to explain the PV diversification. This review will provide a quick overview of the genomes and structures of BPV as well as a more detailed description of genotypic diversity.

Introduction

The historical importance of oncogenic viruses is well documented the brief history and classification of the bovine papillomavirus was summarized here for a better understanding of evolutionary transition of oncogenic viruses. The first report of papillomaviruses occurring in cattle, cottontail rabbits and domestic rabbits were described by (Shope, 1933; Black, 1963.) All bovine papilloma viruses are classified in to four genera *Delta papillomavirus* (BPV-1, 2, 13 and 14), *Epsilon papillomavirus* (BPV-5 and 8), *Xi papillomavirus* (BPV-3, 4, 6, 9, 10, 11, 12 and 15) and *Dyoxi papillomavirus* (BPV-7) (Silva *et al.*, 2016). The BPV types recognized so far are strictly species-specific but BPV type-1 (BPV-1) and BPV type-2 (BPV-2) are the exceptional viruses that can jump the species barrier and cause cross-infection in equids and are called sarcoids. (Nasir and Campo, 2008). BPV-1/-2 was also detected in giraffe, zebra, buffaloes and yaks. The epidemiological studies on

the bovine papillomavirus reveal BPV-1 and 2 as the most frequently identified virus types (Santos *et al.*, 2014).

Genome of Papillomaviruses

Bovine Papilloma viruses are small, circular, double-stranded DNA viruses. The BPV genome is almost 8 Kb in size and is organized into three regions: early (E), late (L), and long codon region (LCR), The E region codes for replication proteins (E1, E2, E4) as well as oncoproteins (E5, E6, and E7) (Bocaneti *et al.*, 2016). The viral capsid structure is constituted by two proteins encoded by the late genes in viral genomes. The L1 gene is useful for classification and construction of phylogenetic trees (Bernard, 2006). The capsid is formed by 360 copies of L1 protein, organized as 72 capsomers (pentameric assembled), and 12 copies of L2 protein. Although being present in less number, L2 minor capsid protein is necessary for viral morphogenesis. The L region codifies capsid proteins (L1 and L2) (van Doorslaer, 2013). The LCR does not codify any protein but has the origin of replication (*ori*) (van Doorslaer, 2013). The Phylogenetic classification of PVs are based on the L1 open reading frame (ORF) sequence homology, since this is the most conserved ORF among the different PV types (Munday *et al.*, 2015). According to this system, differences over 10% on L1 ORF sequence determine a novel virus type, while differences between 2-10%, a novel virus subtype (de Villiers, 2013). The L1 ORF is the most conserved among PVs (Bernard *et al.*, 2006), and for this reason, it is employed in virus classification (Haga *et al.*, 2013). The L1 protein has 55 kDa (Buck *et al.*, 2,013) and is able to self-organize in pentameric structures that compose the viral capsid (Ribeiro-Müller and Müller, 2014). It has a central role in viral infection mechanisms, allowing the capsid anchorage to heparin sulfate receptors present in the cell membrane (Florin *et al.*, 2012). L1 is a late protein and expressed in the most differentiated epithelium layers (Buck *et al.*, 2004). Therefore, L1 immunodetection has been considered the main evidence of productive infection. The L2 protein binds to viral DNA, contributing to encapsidation and then to viral release (García-Vallvé *et al.*, 2005; Campo, 2006).A third structural protein (L3) has been described as present exclusively in BPV-4 (Catroxo *et al.*, 2013). However, its function remains unclear. The non-oncogenic early proteins expressed by papillomaviruses are E1, E2.& E4. The E1, E2 ORFs are expressed after PV infection and are essential for virus replication (Ferraro *et al.*, 2011). The E1 ORF is the second most conserved sequence among the PVs (Forslund *et al.*, 1999; Enemark *et al.*, 2000), and codifies the E1 protein. Its helicase activity can induce simple strand breaks (SSBs) and double-strand breaks (DSBs) in host DNA (Schuck and Stenlund, 2015). The E4 ORF codifies a family of proteins produced by splicing followed by post-translational modifications (Campo, 1997). The E4 protein is the most expressed protein of PVs (Doorbar, 2013). E4 is associated with virus maturation and extracellular matrix (MEC) remodelling (Ferraro *et al.*, 2011). The E5 is an oncoprotein and its transforming potential is known since 1960 (Roberts, 2015). The E5 oncoprotein can induce both *in vivo* and *in vitro* transformation (Campo, 2006; Silvestre *et al.*, 2009; Rampias *et al.*, 2013; DiMaio, 2014). E6 causes cytogenetic damages and stimulates necrosis (Araldi *et al.*, 2015). The E7 oncoprotein has 127 amino acids and induces DNA breaks, contributing to cell cycle deregulation (Park *et al.*, 2014.).

BPV Diversity

The present PV diversity can be explained by multiple evolutionary mechanisms (Gottschling *et al.*, 2007). Virus host-divergence is an important evolutionary force, however this force solely cannot explain the evolution of PVs and their diversity, thus alternative mechanisms such as within-host virus duplication, recombination, viral sorting, or viral adaptation after a host switch, may therefore contribute considerably to explain the PV diversification. For BPVs, at least three lineages seem to originate the currently known types. These lineages probably passed through a prior divergence process preceding the host divergence. This could

also explain the proximity of BPVs to PVs that infect distantly related hosts. In addition, zoonotic transmission of PVs is rare event but it occurs in BPVs as they were found in zebras, horses and buffaloes (Silvestre *et al.,* 2009; van; Bogaert *et al.,* 2008). Other evolutionary mechanisms could be associated with BPV diversification,

BPV Detection and Distribution

A variety of polymerase chain reaction (PCR)-based techniques is used to detect BPV DNA. These PCRs are often predicated on detecting one or two BPV types utilising type-specific primers. Real-time detection or sequence analysis (Brandt *et al.,* 2011) or restriction fragment length polymorphism (RFLP) analyses of the produced PCR fragments are used for genotyping. There have also been reports of consensus primers capable of recognizing perhaps more than two BPV types (Ogawa *et al.,* 2004). Furthermore, PCR techniques initially developed to identify human papillomaviruses have been utilized to genotype distinct BPV types.PCR assays that amplify partial fragments of the L1 gene, followed by sequencing, have suggested the existence of numerous yet uncharacterized BPV types in cattle herds from diverse geographical regions.

Transmission of BPV

Warts are usually spread through direct contact or indirectly through fomites left on surfaces. Many causes, including contaminated food and equipment, such as halters, nose leads, grooming and earmarking objects, and so on, as well as inheritance, nutritional imbalance, and a hormonal imbalance that inhibits the immune system, may all play a role in the disease's spread (Campo *et al.,* 1994; Nicholls and Stanley 2000). It is well understood that confined populations are more vulnerable due to virus transmission via direct (skin to skin or animal to animal) or indirect (infected objects) contact Nasir and Campo, 2008). Apart from the well-established skin-to-skin method, alternative route of infection, such as arthropod vector and vertical transmission, has been proposed (Freitas *et al.,* 2003; Finlay *et al.,* 2009). However, these alternatives via transmission might be less efficient (Bravo *et al.,* 2010). In addition, the occurrence of horizontal transmission of BPV 2 has been reported in the healthy cattle experimentally inoculated with peripheral blood from hematuric animals (Stocco dos Santos *et al.,* 1998). Recent findings of BPV in epidermis and formation of L1 capsomers of equine sarcoid and active BPV in normal skin of equine (Bogaert *et al.,* 2008; Brandt *et al.,* 2011) could help to explain the occurrence of equine sarcoid in animals kept far away from any bovine virus source, especially when living in close contact with other affected equids (Brandt *et al.,* 2011). It is believed that flies can be a vector for BPV and transmit the virus between bovine and horses. Although the papilloma usually regresses spontaneously without significant scarring, they occasionally can persist and progress to squamous cell carcinoma, hence intervention is indispensable (Campo 1997). Successful treatment of cutaneous papillomatosis has been a great challenge because effective medicines are not available. Several treatment options like antimony preparations (Tailor *et al.,* 2017; Satheesha *et al.,* 2018), homeopathic drugs (Tailor *et al.,* 2017; Paksoy *et al.,* 2015), autohaemotherapy (Chand *et al.,* 2018;), autogenous vaccines (Vadalia *et al.,* 2013; Ranjan *et al.,* 2013; Turk *et al.,* 2005) and immunomodulators like Ivermectin (Börkü *et al.,* 2007; Puvarajan *et al.,* 2016 and Levamisole (Paksoy *et al.,* 2015; Ciam *et al.,* 2007; Pattar and Priyanka 2013) have been tried with varying degree of success. The information regarding the actual genotype diversity in non-human vertebrates is still far less reported than that of HPVs. The accurate detection of the type of genotype involved in an infected case represents one of the main strategies for controlling the virus. Generally, a tentative diagnosis is made based on clinical signs, while a confirmative diagnosis relies on Molecular techniques, histopathology, immunohistochemistry, & electron microscopy of the specimens.

Bovine papillomavirus is a group of viruses extensively studied in the last several years& has

always been considered as an excellent experimental model to investigate HPV infection and carcinogenesis. In this review, we broach new insights into the mechanisms of BPV co- infection, cross-species infection and transmission. New aspects involving the mechanisms of BPV transmission and cross-species infection have broken some paradigms about these viruses. The BPV status as an epitheliotropic and species-specific viruses can no longer be seen that way. The heterologous BPV infection has been consistently documented by several research groups worldwide. The sequencing data of papillomaviruses infecting animal species are vastly underrepresented Even the entire range of hosts is not well defined. Non-human vertebrate genotype diversity is still far less well-documented than HPV genotype. One of the primary strategies for virus control is the accurate detection of the genotype involved in an infected case.

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