Papillomaviruses in Domestic Cats

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Papillomaviruses (PVs) are well established to cause hyperplastic papillomas (warts) in humans and animals. In addition, due to their ability to alter cell regulation, PVs are also recognized to cause approximately 5% of human cancers and these viruses have been associated with neoplasia in a number of animal species. In contrast to other domestic species, cats have traditionally been thought to less frequently develop disease due to PV infection. However, in the last 15 years, the number of viruses and the different lesions associated with PVs in cats have greatly expanded.

Keywords: cats ; felid ; papillomavirus ; review ; cancer ; viral oncogenesis ; skin

1. Introduction

Papillomaviruses (PVs) are double-stranded circular DNA viruses. Their genome contains five or six early (E) genes and two late (L) genes. With rare notable exceptions, PVs are species specific and PVs often show tropism for certain types of epithelium and even specific locations on the body [1]. PVs are classified using the highly conserved L1 gene. If two PVs have 60–90% similarity in the L1 open reading frame (ORF), then they are considered to be different types while less than 60% similarity suggests that the PVs are likely to be within different genera [2]. Members of a genus often infect closely related host species and often result in similar lesions within that host [2]. Papillomaviruses have been found to infect almost all species that have been studied including mammals, birds and reptiles [3]. Most species are infected by multiple PV types, often within multiple different genera [2].

The PV life cycle is coordinated with the normal division and differentiation of cells within mucocutaneous stratified epithelium [4]. Microtrauma initially allows the PV to gain access to the basal cells. Expression of the PV E1 and E2 genes results in the virus creating a small number of copies of itself which then infect surrounding basal cells [4]. The infection of basal cells allows persistence of PV infection, but viral replication is only possible when a basal cell terminally differentiates and moves into the suprabasilar layer of the epithelium [4]. Here, due to the expression of the E6 and E7 proteins, the PV interferes with cell regulation by preventing the cells from terminally differentiating, ensuring the nucleus is retained, and forcing the epithelial cells to divide and make copies of the PV [4]. As the infected cells near the surface of the epithelium, the L1 and L2 proteins are expressed, allowing the virion to be assembled. Cells slough from the surface of the epithelium and normal epithelial cell degeneration releases the viral particles into the environment [4].

Whether or not infection by a PV will result in a visible lesion is dependent on the amount of epithelial replication (and thus viral replication) that the PV is able to stimulate. For the majority of PV infections, the virus replicates slowly, resulting in a mild increase in epithelial cell replication which is not detectible clinically [5]. Such asymptomatic infections appear to be ubiquitous in humans and are probably also extremely common in the domestic species [6]. In contrast, a minority of PV types rapidly replicate and stimulate marked epithelial replication. The resultant thickening and folding of the epithelium is visible as a hyperplastic viral papilloma (wart) [1][7]. Warts develop due to rapid viral replication and massive numbers of viral particles are produced in the affected areas of epithelium.

As PV infection does not cause cell necrosis and the majority of the effects of the virus are in the more superficial layers of the epithelium, PVs tend to stimulate a mild inflammatory response. This is especially true for the PVs that replicate slowly and are asymptomatic [8]. When a response is made by the body, the body detects and attacks infected cells by developing a cell-mediated immune response [9]. This immune response is able to limit PV replication and, due to the loss of PV proteins influencing cell growth, any hyperplastic lesion induced by the infection will resolve. The time of onset of the cell-mediated immune response is variable [9]. This variability explains why, although most oral papillomas in dogs will spontaneous resolve in 3 months, others will persist for up to a year [10]. However, while the immune response results in lesion resolution, PVs are able to persist in the basal cells and probably continue to replicate at a low rate. The role of the immune system in controlling PV replication is demonstrated by the lack of any visible lesions due to the ubiquitous infection of the skin by the human *betapapillomaviruses* in immunocompetent people [6]. However, these same viruses are able to cause multiple hyperplastic plaques on the skin when people are immunosuppressed [11]. Likewise, chronic

immunosuppressive therapy in dogs has been reported to predispose to PV-induced pigmented plaques of the skin [12]. Infection by a PV also results in the production of serum antibodies. These do not appear to influence lesion resolution, but protect against subsequent infection by that PV type [13].

In addition to the development of hyperplastic papillomas, the ability of PVs to alter cell regulation means that they can also influence the development of cancer [4]. In people, PVs are the most common viral cause of cancer with the high-risk *alphapapillomaviruses* causing approximately 5% of all human cancers including most cervical squamous cell carcinomas (SCCs) as well as a significant proportion of oral SCCs [14]. Likewise in the domestic species, PVs have been associated with neoplasia in horses, dogs, cattle, pigs, and sheep [15][16][17][18][19]. However, it is important to recognize that the vast majority of PV infections in humans and animals do not result in the development of neoplasia. It appears that additional factors such as the speed of the immune response or the presence of other promotors of neoplasia are critical in determining whether or not a PV infection will result in cancer [8][20].

As in other species, the majority of cats are infected by PVs [21]. However, PV-induced disease appears to be rare in cats compared to the other domestic species [22]. This review briefly discusses the methods used to investigate a potential PV etiology within a lesion. The seven fully sequenced PV types that are currently recognized to infect cats are then reviewed. The diseases associated with PVs in cats are described and the review ends with the potential to use vaccines to prevent PV-induced diseases in cats.

2. Prevention of Papillomaviral Disease in Cats

A proportion of feline cancers appear to be caused by PVs. Therefore, these cancers could be prevented by preventing infection by the causative PV. In human medicine, PV vaccines are used to prevent PV-induced papillomas (warts) as well as PV-induced genital and oral cancers [23]. While vaccines have been highly successful in humans, the use of vaccines faces some significant challenges in cats. Firstly, to be effective a vaccine has to be given prior to first infection. This is easy for the human PV vaccines as the causative PV types are spread by sex, providing an ample window of time in which to vaccinate. In contrast, cats have been shown to be infected by FcaPV2 within the first few days of life [21] making it difficult to vaccinate cats prior to first infection. Recently, a virus-like-particle vaccine against FcaPV2 was developed and used in adult cats [24]. Due to the ubiquitous nature of FcaPV2 infection all cats were already infected by FcaPV2 at the time of vaccination. While vaccination resulted in a 7-fold increase in antibody titres in cats, the increased antibodies did not reduce viral load. If the viral load influences which cats will develop lesions due to FcaPV2, these results suggest that vaccinating a cat that is already infected by FcaPV2 will not influence disease development [24]. In an experimental setting it may be possible to vaccinate kittens prior to being first infected. However, these vaccines do not appear to be a practical way to prevent PV infection in more general veterinary medicine. The lack of reduction in viral loads due to vaccination also suggests that a FcaPV2 vaccine would not be useful as a treatment [24]. In people, initial evidence from a number of studies suggested that vaccines could be useful in treating PV-induced warts [25]. However, in a recent study of approximately 500 patients, the use of HPV vaccines was not found to have any statistically significant benefit in the treatment of anogenital warts [26].

While the majority of PV-induced diseases appear to be caused by FcaPV2 in cats, vaccines could be developed against other PV types that infect cats. Infection with BPV14 appears to be rare in cats, suggesting it would be possible to vaccinate against this PV type prior to first infection [27]. As feline sarcoids can result in death of the cat [28], protecting against infection would be valuable. However, feline sarcoids are very rare feline tumors that are limited to cats that have close contact to cattle. Considering the small minority of cats that are susceptible to feline sarcoids and the overall rarity of these tumors, it appears unlikely there would be a commercial market for a vaccine against BPV14.

It is currently unknown when cats are infected by FcaPV1, although evidence from dogs suggests that the oral papillomas probably develop at the time of first infection. If most cats are not infected until adulthood, this would suggest a potential window in which to vaccinate. However, as with feline sarcoids, cats appear to develop these lesions only rarely [29]. In addition, in the small numbers of cats in which papillomas have been detected, these were detected as incidental findings and there is no evidence that oral papillomas cause significant disease in cats [29].

It is also currently unknown when cats are infected with the *Taupapillomaviruses* FcaPV3, 4, 5, and 6. It is possible that infection is later in life, allowing an opportunity for vaccination. However, each of these PV types are currently thought to be rare causes of disease in cats. Furthermore, a vaccine would need to be given for each type as the currently used PV vaccines do not provide cross-protection against different PV types [23]. The need to include multiple virus types would increase the cost of any vaccine and, considering the rarity of disease caused by these PV types, a vaccine is unlikely to be commercially viable.

3. Conclusions

While domestic cats have been comparatively recently recognized to develop clinical disease due to PVs, knowledge of the range of PV types that infect cats and the different lesions that are caused by infection has expanded rapidly in recent years. It appears likely that additional FcaPV types will be identified in the future and it is possible that a role of PVs in other diseases in cats may be identified. Currently, preventing PV infections in cats appears to be difficult. As all cats are infected by FcaPV2 and potentially the other FcaPV types, it may be better to investigate ways of preventing a normal asymptomatic infection from progressing to a hyperplastic or even neoplastic disease. To do this, the underlying changes to the host that allow proliferation of PVs and subsequent disease development need to be better understood. Thus, the aim of future research may be to better understand the critical interactions between the feline host and PVs.

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