New insight in papillomavirus-induced skin and mucous membranes carcinogenesis in animals

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Papillomaviruses (PV) are small DNA viruses that induce a wide variety of skin and mucous membrane hyperplastic lesions. They are considered important carcinogens in humans and some high-risk PVs are directly responsible for the development of cervical cancers in women [1]. On the other hand, the role of PVs in the development of cutaneous squamous cell carcinoma (SCC) is not as definite [2]. There is however emerging epidemiological evidence to suggest that PV might play an important role in skin cancerogenesis, especially in epidermodysplasia (EV) associated-one. Evidence also suggests that ultraviolet (UV) radiation contributes to the cancerization of some PV-associated skin cancers [3]. Some animals models support the causative role of PV in the induction of skin SCC: A few decades ago, it was demonstrated that cottontail rabbit PV (CRPV) are able to induce skin cancers in rabbit [4]. Others studies have also established that attenuated life canine oral PV (COPV) vaccine induce SCC in Beagles [5]. Additionally, canine and feline can be affected by skin conditions that share some similarities with human EV and cancerization has been reported in some patients.

**Epidermodysplasia verruciformis (EV)** is a rare human genodermatosis characterized by multiple flat warts caused by so-called EV associated PV [6]. A major clinical complication of EV is the development of squamous cell carcinoma (SCC) which is reported in 30 to 50 % of affected people [7]. A similar condition is observed in immunocompromised people. Additionally, EV-like diseases have been described in the dog and cat [8, 9].

**Canine pigmented viral plaques**

A few years ago Nagata described cases of canine viral pigmented plaques and suggested that the condition could be the counterpart of human EV[8]. Fourteen cases of this condition have now been reported. Affected dogs usually present pigmented macules or slightly hyperkeratotic plaques. Carcinomatous transformation (In situ and invasive carcinomas) has been frequently reported in affected dogs (6 out of 14 cases).

**Feline viral plaques**

Feline viral plaques in older or immunosuppressed cats bear also similarities with human EV or canine pigmented viral plaques [9]. Dysplasia or atypia is not present but feline viral plaques often coexist in the same animal with Bowenoid in situ carcinomas. As PV antigens have been uncovered in both lesions on same animals, feline viral plaques could be regarded as precursory lesions of Bowenoid in situ carcinomas (BISC) [10, 11].Positive immunohistochemistry in BISC lesions supports a causative role of PV in the development of the lesions [12].

**Skin SCC in dogs**

A few years ago, Bregman and coworkers reported that attenuated life COPV vaccine induced skin SCC in 12 out of 500 treated beagles [5]. Several other studies carried out using PCR and/or immunohistochemistry concluded that 5 to 30% of canine SCC harbour PV antigens or nucleic acids [13] Goldschmidt.
detected additionally a novel virus, namely CPV2, in numerous warts and SCC of several immuno-compromised Beagles [14].

**Skin SCC in cats**

Two different studies have demonstrated the presence PV DNA in feline BISC and invasive SCC [15]. One of these studies also suggested that the positive samples were infected by PV of great genetic diversity. One of this virus has been additionally recently described [10]. IHC studies have confirmed the causal association between virus infection and development of the disease [12].

**PV-induced cell transformation**

Three early PV genes code for the transforming proteins E5, E6 and E7 but not all PVs are able to immortalize and transform epithelial cells. Further, substantial differences exist in the transforming properties of oncoproteins. E5 proteins are small polypeptides with transforming properties. They are the major oncoprotein of bovine PV [16]. They induce transformation by enzymatic functions, such as activation of several kinases [16]. The open reading frame coding for E5 is often deleted in cervical carcinomas in women, indicating that this gene does not play an essential role in maintaining the oncogenic phenotype in such cancers [17]. The role of E5 in the development of skin cancer in humans, dogs and cats is unknown.

As they play a major role in the development of cervical cancer in women, transforming and immortalizing properties of E6 and E7 have been extensively studied. The development of such cancer has been linked to persistent infections with high-risk HPV and is generally preceded by a lengthy latency period [18]. As low-risk HPV genome usually remains episomic, genomic integration is one of the key-events of the carcinogenesis induced by high-risk HPV [19]. After integration, E6 and E7 expression is maintained but regulatory E2 is deleted. The absence of E2 expression provides a growth advantage to affected cells [19]. E7 protein interacts with retinoblastoma tumor suppressor protein (pRb) and related pocket proteins such as p107 or p130. These proteins regulate the activities of transcription factors (E2F family) that control the cell cycle. Additionally, E7 alters cyclin expression (p21 CIP1, p27 KIP1). All in all, E7 contributes to creating and maintaining a replication competent cellular milieu [18, 19].

On the other hand, the E6 of high-risk mucosal HPV bind the p53 tumor suppressor protein as part of a complex with the ubiquitin ligase, E6AP, leading to the rapid turnover of p53 [20]. As p53 is a potent inhibitor of cell growth, arresting the cell cycle at several points, and under some circumstances, activating the apoptotic machinery, its destruction is a major event in the transformation and immortalization [21].

Additionally, E6 and E7 induce cell immortalization through activation of telomerase activity and genomic instability through induction of centrosome abnormalities [19].

Interestingly, the E6 of cutaneous HPV does not bind p53 and does not promote its degradation [22]. Furthermore, p53 is very often mutated in human skin cancers and these mutations are characterized by a specific signature attributed to ultraviolet radiation [23]. E6, in turn, targets bak for degradation and inhibits UVR-induced apoptosis [22]. These findings emphasize that cutaneous HPV-E6 contribution to skin cancerization is markedly different from that of mucosal high-risk HPVs.

The association of HPV and genital cancer is now well established with many lines of evidence supporting the causative relationship [2]. On the other hand
emerging evidence suggests that cutaneous HPVs, including EV-HPV are not able to induce keratinocyte immortalization [22]. Cooperation between UV light and HPV is probably mandatory for skin oncogenesis.


