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HPV vaccination for prevention of skin cancer

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Cutaneous papillomaviruses are associated with specific skin diseases, such as extensive wart formation and the development of non-melanoma skin cancer (NMSC), especially in immunosuppressed patients. Hence, clinical approaches are required that prevent such lesions. Licensed human papillomavirus (HPV) vaccines confer type-restricted protection against HPV types 6, 11, 16 and 18, responsible of 90% of genital warts and 70% of cervical cancers, respectively. However, they do not protect against less prevalent high-risk types or cutaneous HPVs. Over the past few years, several studies explored the potential of developing vaccines targeting cutaneous papillomaviruses. These vaccines showed to be immunogenic and prevent skin tumor formation in certain animal models. Furthermore, under conditions mimicking the ones found in the intended target population (i.e., immunosuppression and in the presence of an already established infection before vaccination), recent preclinical data shows that immunization can still be effective. Strategies are currently focused on finding vaccine formulations that can confer protection against a broad range of papillomavirus-associated diseases. The state-of-the-art of these approaches and the future directions in the field will be presented.

Keywords: cutaneous papillomaviruses, non melanoma skin cancer, vaccination

Abbreviations: BCC, basal cell carcinoma; EV, Epidermodysplasia Verruciformis; HPV, Human Papillomavirus; NMSC, non melanoma skin cancer; SCC, squamous cell carcinoma; VLP, virus-like particle.

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Introduction

Papillomaviruses (PVs) infect keratinocytes of the skin and mucosa of different vertebrate species, including humans. Up to date there are more than 170 human papillomavirus (HPV) types known, which are associated with different clinical manifestations.[1] Genital HPVs cause diverse lesions ranging from benign warts (for low-risk HPV types) to different malignancies (for high-risk types) of which cervical cancer is the most prominent.[2] On the other hand, the wide range of cutaneous HPV types has been associated with diverse skin diseases.[2] Notably, recent metagenomics analysis even show that the highest prevalence of HPV is found in the skin (61%), followed by the vagina (41.5%), mouth (30%) and gut (17.3%).[3]

Many cutaneous HPVs, mainly HPV 2, 7, 27 and 57 (α genus), HPV 4 and 65 (gamma genus), and HPV 1 (mu genus) cause benign papillomas in the skin of which the most frequent entities are common warts (*verrucae vulgaris*), plantar warts (*verrucae plantaris*) and flat warts (*verrucae plana*).[4,5] They affect almost one every 3 schoolchildren[6] and represent a serious burden for immunocompromised patients, especially organ transplant recipients (OTR), who suffer from confluent wart formation all throughout the body. The prevalence in this population was reported to be 48–92% in the first 5 y after immunosuppression.[5] Therefore, although skin warts are benign, they cause a significant inconvenience for the patient, with a clear impact on public health.

On the other hand, HPVs from the β genus are suspected to play a role in the development of non-melanoma skin cancer (NMSC). NMSC, which comprises basal cell carcinoma (BCC, approximately 80% of cases), squamous cell carcinomas (SCC, approximately 20% of cases) and other less frequent entities, is the most frequent malignancy in the Caucasian population.[7] The main risk factor for NMSC is exposure to UV radiation, since more than 80% of the lesions appear in sun-exposed areas. Another important risk factor is immunosuppression, with SCC

appearing 65–250 times more frequently in OTR than in the general population.[8] Additionally, although still controversially discussed, meta-analysis of the current literature shows cumulative evidence that infection with certain cutaneous HPVs can be a cofactor for the development of NMSC, especially SCC.[9-11]

The oncogenic potential of β-HPV infection (e. g. HPV5 and HPV8) in NMSC has been originally identified in patients suffering from the rare inherited disease Epidermodysplasia Verruciformis (EV), who are characterized by an increased susceptibility to cutaneous HPV infection.[12] These patients apparently display an inherent genetic predisposition, harboring autosomal recessive mutations in the EVER1 and EVER2 genes which have been linked to the disease.[13] The transforming potential of the EV-HPVs has not only been shown in transgenic mouse models,[14,15] but also in organotypic raft cultures where EVER2-null keratinocytes can generate a hyperplastic epithelium that favors HPV8 replication.[16]

Additionally, β-papillomaviruses have also been detected in NMSCs of non-EV patients, although usually with very low viral loads. Different studies have reported HPV DNA in 30–50% of NMSCs from immunocompetent patients,[17,18] whereas in lesions from immunosuppressed patients this figure goes up to 90%.[19] These viruses can also be found in premalignant lesions, such as actinic keratosis, where the virus is transcriptionally active,[20] and also in normal skin and plucked eyebrow hairs, where several studies have found an association between presence of viral DNA and increased risk of NMSC.[17] Remarkably, there seems to be an inverse correlation between viral load and the malignancy of the lesion,[21] supporting a hit-and-run mechanism of carcinogenesis[8] that is in contrast to the direct carcinogenic effect of genital HPVs. In other words, since some tumors either lack HPV or only one every 10–1000 cell can be found to be virus-positive, the viral oncoproteins are not necessary to maintain a proliferative and tumorigenic phenotype.[22] In addition to reports focused on the correlation between β-PV DNA and disease, numerous seroepidemiological studies have also contributed data suggesting an association between β-PV infection and NMSC or its precursors.[23-26]

Considering a causal function of β-HPV in cancer formation, several studies have identified different transformation mechanisms that may explain a viral contribution to carcinogenesis. High-risk genital HPV types are known to degrade p53, thereby blocking downstream pathways such as apoptosis.[27] Although β-PV E6 protein cannot exert this direct function, it has recently been shown that the E6 proteins of some β types can inhibit HIPK2-mediated phosphorylation of p53 at serine residue 46 in response to UV damage.[28] This prevents the stabilization of p53 in response to genome destabilizing events[29] and blocks the transactivation of p53 target genes (i.e., MDM2, p21 and proapoptotic genes).[30] Additionally, β-PV E6 targets the pro-apoptotic protein Bak for degradation.[31,32] These effects, usually combined with mechanisms that delay DNA repair (like abrogation of ATR activity[33]) or impairment of the telomere/telomerase system[34] may explain β-PV contribution to skin carcinogenesis by favoring the accumulation of UV damaged cells. The oncogenic potential of β-PV has also been shown in *in vivo* transgenic models which develop SCC in response to β-PV gene expression, either spontaneously or after UV irradiation.[14,35]

Although mortality from NMSC is rare in the immunocompetent population, this malignancy represents a considerable burden on the health-care system, particularly when considering immunosuppressed patients.[7] It is estimated that up to 40% of OTR will develop skin cancers, 90% of which are BCC and SCC, within the first 10 y of transplantation, and up to 80% will do so after 20 y[36] Additionally, skin malignancies are more aggressive in OTRs, with only 56% of 3-year disease-specific survival.[37] Therefore, a prophylactic strategy that could prevent or reduce the impact of these skin manifestations is much needed.

HPV Vaccines

Vaccination against genital HPV types is currently being used worldwide to prevent infection and, in turn, the development of HPV-induced lesions in the mucosa. The two licensed vaccines are composed of the L1 major capsid protein of HPV which has the ability to self-assemble into highly repetitive virus-like particles (VLPs).[38] One vaccine consists of VLPs of HPV16 and HPV18, the 2 more prevalent types causing cervical carcinoma, the other additionally contains VLPs of HPV6 and HPV11 to prevent the development of genital warts. Clinical trials showed a 100% efficacy in preventing HPV16-and HPV18-associated dysplasia in women who had no evidence of infection at enrolment,[39] and the protection elicited was long-term, lasting for at least the first 8.4 y after vaccination.[40] Several lines of evidence suggest that vaccine-induced neutralizing antibodies are the primary mediators of the protection elicited by these HPV vaccines, protecting from a subsequent infection by the targeted HPV types and therefore conferring sterilizing immunity.[41]

Although these vaccines are very effective, they also have several limitations: (i) they target only 2 mucosal high-risk types, therefore potentially preventing approximately 70% of the cervical cancer cases, which leaves 30% of the cases unattended; (ii) they do not target any cutaneous type; (iii) they are very costly, making implementation of wide-covering vaccination schedules difficult in less affluent countries. A VLP-based nonavalent vaccine, which targets 5 extra genital high-risk types, is currently in clinical trials to bridge the gap for cervical carcinoma causing types.[42] Although such a vaccine would increase the rate of protection to theoretically protect against more than 90% of cervical cancer cases, it is unlikely to decrease the already very high costs of HPV vaccination and, additionally, it would still not target any cutaneous type associated with skin warts or NMSC.

L1 Vaccines Against Cutaneous PV Types

The first studies which assessed the potential as prophylactic vaccines of L1-based particles from cutaneous HPV types were focused on analyzing the elicitation of neutralizing antibodies in response to

vaccination. Senger et al.[43] explored the immunogenicity of capsomeres and VLPs from HPV α types 2, 27, and 57, the most frequent causative agents of skin warts. Antibody responses in mice resembled those observed upon vaccination with HPV 16 L1-based antigens and were type-restricted in their *in vitro* neutralizing capacities, as it has been observed for genital HPV types. Combination of the 3 antigens in the vaccine triggered an antibody response capable of efficiently neutralizing all 3 types. In another study, Handisurya et al.[44] studied the serological relationship between VLPs from HPV β types 5, 8 and 92. Again, antibody responses in rabbits were comparable with the ones elicited by genital-types VLPs and, in this case, a limited degree of cross-neutralization could be evidenced.

However, to test a vaccine in a preclinical setting, the mere measurement of appearing antibodies is not sufficient. In other words, to show the efficacy of a vaccine, appropriate *in vivo* read-out systems are required where skin tumors are prevented in a natural host. Evidence that a VLP-based vaccine against cutaneous papillomaviruses can indeed avoid spontaneous skin tumor formation even under immunosuppressed conditions came recently from the animal model *Mastomys coucha*.[45] These rodents are naturally and persistently infected with a cutaneous PV[46] and spontaneously develop not only benign skin tumors, such as papillomas and keratoacanthomas, but also squamous cell carcinomas for which the *Mastomys* PV is the etiological agent.[47] Infection occurs early in lifetime, similarly to cutaneous HPVs, and high viral loads can be detected in the skin of older animals, which trigger the onset of tumor development (**Fig. 1**). Although other reliable animal systems exist (e.g. the cervicovaginal murine challenge model or the cottontail rabbit model),[48,49] *Mastomys coucha* allows to study the impact of a skin papillomavirus in an immunocompetent animal, starting from primary infection in newborns until the final manifestation of a tumor in a natural host. Moreover, in contrast to mice or rabbit inbred strains, the outbred character of these animals does not only mimic the genetic heterogeneity in humans, but also allows determining whether a VLP vaccine is readily protective and finally of translational importance for patients.

In a recent study, we evaluated the efficacy of a VLP-based vaccine on either previously or newly established infections in *Mastomys coucha*.[45] Upon inoculation, the VLPs induce a long-lasting response of neutralizing antibodies that confers protection against benign as well as malignant skin tumors even under systemic immune suppression. Notably, protection includes the maintenance of a low viral load in the skin by an antibody-dependent prevention of virus spread. These results prove the principle that VLPs elicit an effective immune response in the skin under immunocompetent and immunosuppressed conditions in an outbred animal model, irrespective of the infection status at the time of vaccination. This may provide the basis for follow-up studies that should finally lead to the clinical implementation of a vaccine against cutaneous HPV-induced tumors to avoid SCCs especially in OTR.

Second Generation Vaccines and Future Directions

Since there are several cutaneous HPV types potentially involved in the development of non-melanoma skin cancer in humans,[50] a broadly protective vaccine would be ideal. The papillomavirus minor capsid protein L2, contains a major cross-neutralizing epitope that could be used to develop a second generation vaccine.[51] However, L2-derived linear peptides are in general weakly immunogenic, which is why different strategies have been explored to overcome this poor immunogenicity, such as conjugation of L2 peptides to a T-helper epitope and a Toll-like receptor ligand,[52] concatemer formation of multiple L2 peptides,[53] L2 peptide display on structures like bacteriophages[54] or on adeno-associated viruses,[55] chimeric HPV L2 peptide/L1-VLPs[56] or integration into the thioredoxin active site.[57] All these approaches have shown that production of neutralizing antibodies with a broad range of cross-neutralization is achievable, but the titers are usually lower

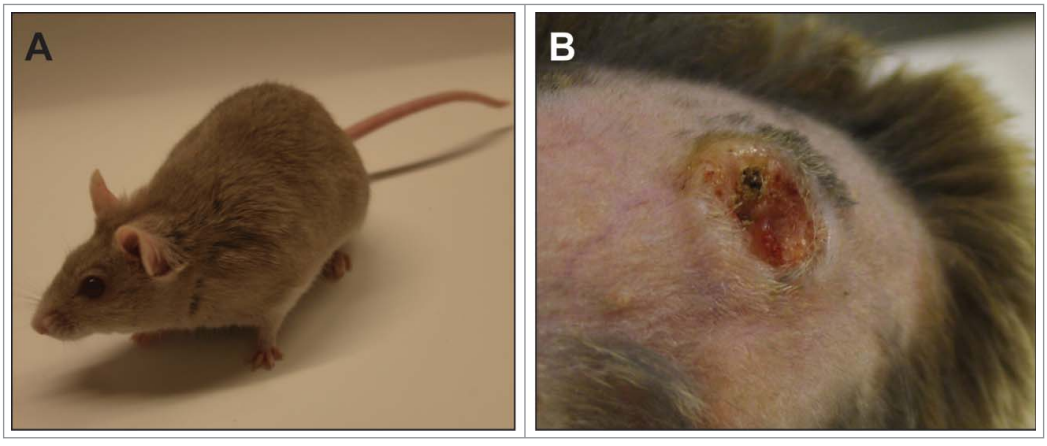

Figure 1. *Mastomys coucha* as animal model for papillomavirus-induced tumors. (**A**) Mastomys coucha. *M. coucha* is an African multimammate mouse of the Muridae family. (**B**) Skin keratoacanthoma. *Mastomys coucha* is latently infected with MnPV, which induces skin tumors in older animals.

than the ones obtained against L1 when using VLPs.

A few studies have focused in the use of an L2-derived vaccine to also extend the range of protection to cutaneous papillomaviruses. Vaccination with an HPV16-derived L2 peptide can generate antibodies which cross-neutralize *in vitro* the non-cognate cutaneous types HPV 2, HPV 3, HPV 5, HPV 8, HPV 23, HPV 27, HPV 38, HPV 57 and HPV 76.[52,58,59] Cross-neutralization could also be achieved *in vivo* by cutaneous challenge with pseudovirions, highlighting the potential of the L2-derived vaccines to confer protection to a broad range of cutaneous HPVs. However, the effectivity of such vaccines in preventing skin tumors has not been assessed so far, and fundamental questions remain to be addressed to confirm the prophylactic potential of these vaccines. One important issue to be answered is whether L2 vaccination can elicit enough neutralizing antibodies to confer protection against tumor formation. Using the cervicovaginal murine challenge model, passive immunization with different dilutions of anti-L1 antibodies apparently interferes with infection at 2 stages (i.e. blocking of the binding to the acellular basement membrane at high titers, inhibition of the association to the epithelial cell surface at low antibody titers).[60] However, there is no direct correlate known between antibody levels elicited by the HPV L1 vaccines and the ultimate protection from lesion development. Therefore, although L2-vaccines generate lower neutralization titers as compared with their L1 counterparts, there is a high chance that these titers are enough for tumor prevention. However, there is still the need to prove such a vaccine in a preclinical model in which spontaneous development of PV-induced tumors can be used as a read-out. For this, *Mastomys coucha* stands out as an excellent animal system to test this new generation of vaccines. Being infected with both a cutaneous and a mucosal PV type,[46] *Mastomys* provides the possibility of not only assessing whether the antibody level raised by an L2-vaccine is sufficient, but also of testing for the first time whether a vaccine targeted against the L2-peptide of one PV-type can prevent tumors caused by an unrelated type under normal and immunosuppressed conditions.

In conclusion, there is currently a large body of results in preclinical models pointing to the fact that a vaccine against cutaneous papillomaviruses is possible and might prevent HPV-associated skin disease, such as warts and NMSC. However, the high number of both cutaneous and genital HPV types which are linked to human diseases, demands for a vaccine that can protect from all these types at once. In this regard, L2 vaccines are promising candidates, and validation of such vaccines in suitable animal models will provide the basis for the clinical implementation of these prophylactic tools.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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