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Commentary

Moving forward with human papillomavirus immunotherapies

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ABSTRACT

Persistent human papillomavirus (HPV) is the primary etiologic agent of cervical cancer and causes a significant number of vulvar, penile, anal and oropharyngeal cancers. The development of highly effective HPV therapeutic vaccines is a reasonable goal given the recent advances in basic and applied immunology. A number of vaccine strategies designed to induce systemic T cell responses have been tested in clinical trials against high grade cervical or vulvar high grade neoplasia and cancers, but with limited success. In line with the emerging trend to focus more on the epithelial context of HPV infection and premalignant disease, it might be advantageous to develop vaccination strategies that promote trafficking of HPV-specific T cells into lesions and overcome the local immunosuppressive environment. The development of more biologically relevant animal models would improve the preclinical evaluation of therapeutic vaccine candidates. Finally, persistent infection and low grade lesions may prove to be easier

targets for therapeutic vaccines, and these vaccines would likely be commercially viable in high income countries and valuable components in screen and treat programs in low resource settings.

KEYWORDS:

Human papillomavirus | cancer | immunotherapy | therapeutic vaccines | mucosal immunity

Human papillomavirus is a large family of epitheliotropic non-enveloped circular DNA genome viruses. Most HPV infections are cleared, however persistent infection with high-risk HPV, especially types 16 and 18, can lead to the development of intraepithelial neoplasia and carcinoma in the cervical, vulvar/vaginal, penile and anal and oropharyngeal mucosa.[1] Systematic screening programs to detect high grade cervical intraepithelial neoplasia and ablative treatment are effective to reduce the incidence of cervical cancer.[2] Because early detection programs for non-cervical sites are not yet available, malignant lesions or carcinoma are often diagnosed at an advanced stage and often require debilitating treatments. Prophylactic vaccines against high-risk HPV infections are attractive interventions to reduce the burden of HPV-induced neoplasia in the long term. However, in the absence of full vaccine coverage and the presence of large number of women with prevalent infections, the incidence of HPV-induced neoplasia will remain a global health concern for many years. Persistent infection and maintained expression of the HPV oncoproteins E6 and E7 are critical factors in the development of intraepithelial neoplasia and cancers, and therefore constitute promising targets for therapeutic vaccines.[3] The evolution of persistent HPV infection to cancer is a slow process that generally takes several decades upon first exposure, which gives a broad window of opportunity to intervene.

Clinical evaluation of immunotherapeutic interventions against HPV-associated neoplasia

Most clinical trials of therapeutic vaccines and immunotherapies against HPV induced diseases have targeted high grade precancers and cancers of the cervico-vaginal and vulvar mucosa. Numerous available vaccine platforms have been tested (see [4,5] for comprehensive reviews). Most of these vaccines were given systemically or remotely from the site of the lesions. The vaccines platforms evaluated include naked DNA,[6-8]

viral vectors such as vaccinia and MVA,[9-12] bacteria such as oral Lactobacillus,[13] proteins [14-16] and short and long peptides.[17-19] In spite of evidence for the induction of cellular immune responses against E6 and/or E7, these clinical trials showed regression in a subset of subjects, at best. Most trials did not have a randomized placebo control group to establish the rate of spontaneous regression in the trial subjects and so the efficacies of the vaccines were often difficult to estimate. The few randomized controlled trials have demonstrated modestly higher regression rates in the vaccine recipients. To the best of our knowledge, therapeutic HPV vaccines have not been formally evaluated in a randomized phase III trial and consequently none has received regulatory approval.

Perhaps, the most notable response rates were observed in a large trial involving multiple rounds of intracervical or intralesional injection at other genital sites with an MVA vector expressing bovine papillomavirus E2.[20,21] Most subjects experienced clinical and virological cures. However, it is unclear whether induction of an adaptive immune response to E2 or the viral antigens in the lesions was involved in the mechanism of regression, and the need for multiple intralesional injections may prove to be a impediment to wide spread implementation.

In addition to traditional vaccines, adoptive T cell transfer therapy has been recently evaluated in a small number patient with metastatic cervical cancer and showed a correlation between clinical response (3 out of 9 subjects) and persistence of HPV-specific transferred T cells.[22] The study provides important proof of concept that cervical cancers can be susceptible to T cell-mediated effector mechanisms.

Immune modulators based on TLR7/8 agonists have been approved for the treatment of genital warts and basal cell carcinomas.[23,24] The use of Imiquimod for the treatment of CIN2/3 or VIN2/3 has shown limited clinical benefits and topical application was more or less well tolerated depending on the study.[25-27]

Why therapeutic vaccines have shown limited efficacy against HPV associated neoplasia

Multiple reasons could explain the limited success of therapeutic vaccines against HPV-induced neoplasia to date. Numerous clinical trials have shown induction of T cell responses against E6 and E7, but the magnitude of the response induced against HPV antigens might have been insufficient to clear HPV infected or transformed cells. The balance of T cell responses between $CD8^+$ cytotoxic T cells (CTL), $CD4^+$ Th1, Th2, Th9,

Th17 or Treg induced against HPV antigens included in the vaccine might have been unfit to trigger a clinical response.[28,29] In addition, induction of the recently described genital tissue resident memory T cells (Trm) may be critical for highly effective vaccines against HPV infections and their associated cancers.[30]

The modulation of the local immune environment by HPV infected or transformed cells might have prevented T cells to effectively clear lesions. Some of the mechanisms described to participate in immune escape of HPV infected cells to CTL induction and/or killing are MHC dowregulation, defects in class I antigen processing,[31] disruption of the inflammatory cytokine response by keratinocytes,[32] upregulation of inhibitory molecules such as PD-L1 or IL-10,[33,34] evolution of a Th2 skewed helper response during neoplastic progression,[35] and induction of regulatory T cells.[36] Deregulation of local homeostasis such as disruption of the chemokine gradient in situ has been shown to prevent infiltration of lesions by T cells.[37] Loss of Langerhans cells, the primary antigen presenting cells in stratified epithelium, is a common feature in lesions induced by high risk mucosal HPV types.[38] In addition, the microbiota might also play a role in the development of HPV-induced neoplasia and shaping an immune suppressive environment, but its role remains unclear.[39,40]

Finally, most HPV therapeutic vaccines have been given systemically or in a remote mucosal site, which might induce a bona fide response but with limited trafficking to the lesions. Failure of T cells to infiltrate infected epithelium appears to be a major mechanism of immune escape in cervicovaginal HPV infection.[37] With few exceptions, the induction of tissue resident memory $CD8^+$ T cells in the genital epithelium after systemic immunization has not been yet addressed in clinical trials and, optimal regimens and vaccine platforms able to induce genital Trm remain to be defined. Importantly, the exclusion of Trm from the circulation implies that classical blood-based immunomonitoring might not predict their induction.

Improving the efficacy of therapeutic vaccines against HPV

Combination of vaccines with topically administered immune modulators, such as TLR agonists, have been evaluated in preclinical models.[41,42] Such approaches induce local inflammation that can recruit circulating T cells to the lesions and therefore increase the ratio of effector to target cells. In addition, this “prime-pull” approach to enhance the recruitment of T cells to the application site might also render infected and transformed cells more susceptible to killing by CTL and mitigate repressive immune

modulation. It is encouraging that clinical trials of systemic immunization followed by local stimulation with a TLR agonist are underway (e.g. NCT00788164).

Combination of vaccines with systemic administration of an immune checkpoint inhibitor or stimulatory antibodies is an alternative method to overcome direct inhibition of T cells by ligands expressed by tumor cells or APC in the tumor environment. Immune checkpoint inhibitors have been recently approved to treat lung cancer and melanoma and are being evaluated against many other cancer types.[43] Expression of PD-L1 by HPV-infected and transformed epithelial cells has been documented,[33] suggesting that it could prevent infiltration and lysis of infected cells by HPV-specific T cells. Antibodies targeting PD-L1 or its receptor PD-1 on HPV-specific T cells might unleash a T cell response at the lesions. Although current approaches are promising for advanced stage carcinomas, they might not be amenable for treatment of premaligant disease because of the substantial adverse events that are frequently seen with systemic application of immune checkpoint inhibitors.[44] The topical application of immune checkpoint inhibitors on the lesions might mitigate the systemic toxicity of immune checkpoint inhibitor while retaining efficacy. IgG is transported bidirectionally across the cervicovaginal epithelium via the neonatal Fc receptor.[45] Therefore, monoclonal antibodies that inhibit immune check points might reach T cells and other immune cells in the genital submucosa in locally active concentrations after intravaginal application.

In preclinical models, intravaginal vaccination induces large numbers of local antigen-specific intraepithelial T cells, whereas systemic vaccination does not. Viral vector-mediated vaccination at distant mucosal sites, e.g., intranasal, was much less efficient at inducing intraepithelial T cells in the genital tract than intravaginal vaccination.[46,47] A recent pilot clinical trial of CIN2/3 patients compared intramuscular, intradermal and direct intralesional injection of a naked E6/E7-expressing plasmid DNA vaccine. Consistent with the preclinical studies, intralesional $CD8^+$ T cell infiltrates increased after intralesional, but not after intramuscular or intradermal injection.[48] However, there was no difference in the limited clinical and virological responses observed with the 3 routes of delivery. An interesting question is whether it is preferable to introduce a vaccine directly into the HPV neoplastic lesions or elsewhere in the cervicovaginal tract. Intralesional vaccination might maximize the focus of the induced immune cells to the infected cells. However, a local suppressive environment might inhibit induction of an effective immune response, particularly during priming. Since intraepithelial $CD8^+$ T cells are highly mobile within the lower epithelial layers,[49] T cells induced or amplified

at adjacent sites should be able to reach the infected cells. In our opinion, alternative intravaginal vaccination strategies deserve future clinical evaluation.

Need for more accurate preclinical models of HPV persistent infection and low-grade lesions

Numerous preclinical animal models have been used to evaluate therapies against HPV-associated malignancies. Preclinical therapeutic efficacy of vaccines has usually been tested in subcutaneous or orthotopic mouse models in which high numbers of in vitro passaged syngeneic tumor cells are transplanted.[50,51] In spite of the impressive protection displayed by some vaccine candidates in these models, the preclinical findings have not generally translated into clinical efficacy. This discrepancy might be due to differential immunogenicity of the vaccine platforms in mice and humans. In particular, adjusting the dosage of vaccine antigens between mice and humans is difficult to achieve and might lead to over estimating human immunogenicity using mouse models. Also, due to the rapid growth of the transplanted tumor cells and time needed to induce a cellular response, therapeutic vaccine must be given at relatively early stages when the tumors are still small and presumably before immune escape mechanisms are fully developed. In addition, although the in vivo biology of the tumors and the surrounding microenvironment are not well documented, they probably do not closely match those of slowly arising intraepithelial neoplasia in humans.

Current models using E6 and E7 transgenic mice permit the study of the cellular and molecular mechanisms involved in the development of premalignant diseases and immunosuppression at early stages.[52-54] However, the tissue wide expression of E6 and E7 does not reflect their focal expression in human neoplasia, and tissue wide expression of the oncogenes does not permit selective T cell targeting of the transformed cells in the lesions. Genetic models allowing for focal expression of E6 and E7 oncoproteins that drive the in situ development of intraepithelial neoplasia in cervicovaginal, anal or oropharyngeal epithelium would likely be more predictive preclinical models to evaluate immunotherapies and vaccines. Development of this type of models should be a high priority.

Handicapping targets for HPV therapeutic vaccines

Effective therapeutic vaccines would be useful across the entire spectrum of HPV induced neoplasia, from persistent infection and its histological manifestation, grade 1 intraepithelial neoplasia, to malignant cervicovaginal, anal, and oral cancers. Effective

therapeutic vaccines for cancer are the most pressing need. Unfortunately, they will almost certainly be the most difficult to develop, due to the many well documented ways that the genetically unstable tumors can evolve to escape immune surveillance. Most clinical trials of therapeutic HPV vaccines have targeted CIN3 (or CIN2/3), in large part because these lesions (especially CIN3) infrequently regress and, when identified in screening programs, require treatment, currently with ablative therapies.[55] While generally effective, these destructive treatments are associated with a significant number of failures and adverse events. Nevertheless, the general effectiveness and tolerability of current CIN3 therapies places a rather high bar for immunotherapeutic approaches.

In contrast to CIN3, ablative therapy of anal intraepithelial neoplasia (AIN3) is more often associated with substantial morbidity and a more benign immunotherapy would address a large unmet need.[56] Important questions that deserves further inquiry are what proportion of CIN3s and AIN3s are genetically unstable and have already undergone immune selection and whether these features vary by HPV type. The possibility remains that they may be closer to cancers than asymptomatically infected tissues and low grade lesions with regard to susceptibility to immune interventions.

CIN2 is a rather difficult to define intermediate class of lesions that might be an attractive target for immunotherapy because of the current inability to estimate the likelihood that a specific lesion will regress or progress to CIN3.[57] Thus there is an unmet need for a more benign treatment of these lesions.

CIN1/persistent cervical infection has received relatively little interest as a target for HPV immunotherapy. In part, this may be because it is not considered a treatable disease with current therapies. Also, therapeutic efficacy trials would have to be relatively large because of the high rate of spontaneous regression. However, with the increasing adoption of virological-based primary screening for cervical cancer risk in high income countries, there will be increasingly large numbers of women who will be informed that they have a potentially oncogenic sexually transmitted infection, but there is no treatment option for them unless it progresses to a high grade precancer. These women would likely provide a large and motivated market for a therapeutic vaccine, provided it was benign enough for use against infections that have a 90% spontaneous clearance rate. More importantly from an international public health point of view, a safe immunotherapeutic vaccine against persistent infection might greatly facilitate cervical cancer prevention programs in low resource settings that could

involve point of care HPV detection followed immediately by therapeutic (and perhaps also prophylactic) vaccination of women who test positive for oncogenic HPV types.

Importantly, persistent infection/CIN1/AIN1 are likely to be more susceptible to immunotherapies than advanced lesions since they are less likely to be genetically unstable or to have undergone immune selection. Productive infections also provide more viral antigen targets, including E2, which appears to a major T cell target in natural infection.[58] In our opinion, it might be preferable to focus more attention on developing vaccines to treat productive infections, since they are more likely to be successful, and subsequently apply the lessons learned in their development to the presumably more difficult case of more advanced lesions.

Conclusions

There are reasons to be optimistic that development of highly effective HPV therapeutic vaccines can be achieved, including the many recent advances in basic and applied immunonology and the current level of public sector and industry support. However, a relatively large number of reasonable vaccine strategies focused on induction and measurement of systemic immune responses have been tried, but with limited success. It is our opinion that the emerging trend to focus more on the epithelial context of HPV infection and premalignant disease should be strongly encouraged. Efficient trafficking of viral-antigen specific T cells to lesions and overcoming the local immunosuppressive environment once they arrive may be critical components to a successful vaccine. Development of more biologically relevant animal models would increase our ability to rank the potential of various candidates for clinical trials. Finally, we believe that HPV therapeutic vaccine development should move up the disease severity continuum rather that down it, as has been the case historically. In this regard, it seems important for the research community to clearly establish an investment case for vaccines targeting persistent infections, including detailed modeling of efficacy trials, in order obtain sufficient public sector and industry support for these endeavors.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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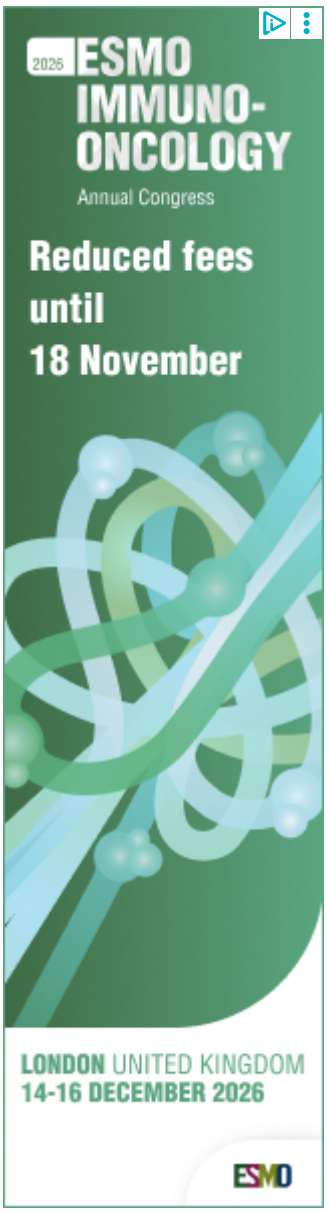
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