Vaccines for papillomavirus infection

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Abstract

Vaccines to prevent PV infection, utilising PV L1 virus like particles (VLPs) to induce neutralising antibody, are in clinical trial and show all the characteristics likely to be associated with success. Results warrant global planning for the deployment of VLP vaccines within a decade, as part of a program to prevent cervical cancer. Vaccines designed to treat existing PV infection by inducing therapeutic cellular immunity targeted to PV proteins are at a much earlier stage of development. The wide choice of potential and proposed antigens, routes and mechanisms of delivery, and possible treatment regimens suggest that, to move the field forward, surrogate markers allowing comparison of the relative efficacy of different vaccine approaches are required. These should be based on reduction in load of virus infection, and need to be validated in animal models or in man.

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1. Introduction

Sophisticated epidemiologic studies reported at the recent 19th Papilloma virus workshop in Florianopolis, Brazil, support the hypothesis formulated 20 years ago by Gissmann and Zur Hausen that papillomaviruses are a major antecedent cause of cervical and other anogenital malignancies. These studies confirm that persistent infection with a high risk genotype of HPV conveys significant risk of anogenital malignancy, to a level where it is reasonable to describe HPV as a ‘necessary’ factor, and demonstrate that the contribution of other identifiable genetic and environmental factors to development of cancer is relatively small. Thus, prevention and control of cervical cancer on a global basis is most easily envisaged through vaccine-mediated prevention of HPV infection, and/or elimination of persistent infection of sites at high risk for development of squamous malignancy.

2. Natural immune responses to PV infection

Generally, effective viral vaccines work through generation of neutralising antibody, and protection is proportional to the amount of antibody available at the virus entry site, and lasts as long as neutralising antibody persists. Larger scale longitudinal studies of papillomavirus seroepidemiology are available only for a limited subset of
genital PV genotypes. These demonstrated that papillomavirus infection naturally induces relatively low titres of neutralising antibody, and that some infected individuals seemingly acquire and clear infection without ever developing measurable antibody. These studies also demonstrate that, following infection, antibodies to PV are largely directed against conformational epitopes displayed on the outer aspect of the virus capsid, and directed to major capsid protein L1. Such antibodies are genotype specific, and mostly of IgG type, and are present only in low titre in mucosal secretions. Nevertheless, the limited epidemiologic evidence available to date suggests that prior infection with a particular PV genotype is host protective against further infection with that genotype, though not with other types. Thus, vaccines to prevent PV infection will likely be designed to induce antibodies directed to conformational epitopes of the L1 capsid protein, and would be predicted to be type specific.

3. Vaccines to prevent PV infection

Perhaps the most interesting vaccine study reported at the Florianopolis meeting was a post hoc analysis by Koutsky and colleagues (O-50)\(^1\) of the results of a number of phase I and II studies of HPV16 specific PV vaccines based on recombinant L1 virus like particles (VLPs). While post hoc analysis is always risky, the results, taken at face value, demonstrate absolute protection (zero cases in 66 subjection) against new incident HPV infections of type 16 amongst individuals vaccinated with a range of doses and formulations of HPV16 VLPs, and several incident cases (nine in 129 subjects) amongst those given placebo vaccine in these studies. Similar numbers of incident cases of HPV infection with other genotypes in both groups confirms that differences are unlikely to be due to chance variation in risk, and also support the type specificity of vaccine induced host protection over at least a year following immunisation. These early results, when combined with the results of several studies showing good safety profiles and almost universal induction of high titres of virus specific antibody by VLP based PV vaccines of types 11 and 16 in human volunteers (O-51, O-53), suggest strongly that PV vaccines are likely to be at least partially effective in prevention of new infection with the high risk PV genotypes. Duration of protection remains to be established, though modelling the decline of antibody titre following vaccination in the early phase human studies (O-50, P90) suggests that protection will persist, like the protection following immunisation with the particle based vaccine for Hepatitis B, for several years if not decades. Animal (P-93) and human studies (O-54) suggest that it should be possible to induce simultaneous protection against many types of PV with multivalent vaccines, though the limits to this have yet to be tested, and priming through past infection with one genotype may limit the ability of the immune system to respond adequately to other types (P-82) incorporated into a multivalent vaccine, an issue not easily resolvable in animal trials. Mucosal antibody seems to be induced by systemic delivery of VLPs (O-52) and can also be induced or boosted by mucosal delivery (P-103) though before this could be considered a preferred delivery route for vaccine in developing countries, protection would need to be demonstrated to be of comparable duration.

Confidence that VLP based vaccines have the potential to prevent PV infection has allowed exploration of how such might be delivered to the developing world, (O-29, O-30), and their cost effectiveness in the prevention of cervical cancer (O-54). A potential advantage to local cheap and simple production of VLPs has led to exploration of production of VLPs in plants (P-75), and the natural immunogenicity of VLPs allows examination of their utility as vaccine delivery vectors for other antigens (P-70, O-55)

Other means of inducing protection against PV infection have been trialled in animals. Polynucleotide vaccines incorporating the L1 gene of PV induce neutralising antibody in beagle dogs (O-148), and codon modification to allow better expression in eukaryotic systems improves immu--

\(^1\) The abstracts cited in this paper are available at www.hpv2001.com.
nogenicity (P-80). Such vaccines are cheap to produce and heat stable, and may overcome some of the difficulties of delivering VLP vaccines to the developing world, where currently no vaccine program accesses women prior to the onset of sexual activity, who would be the primary target of a vaccine designed to reduce cervical cancer incidence through prevention of PV infection. The L2 protein of the PV capsid, while not as effective at inducing immune responses during natural infection as the L1 protein, has been shown to induce immune responses as a part of a vaccine which virus neutralising in vitro (P-96), and may therefore prove useful if a significant number of subjects are proven unable to respond to an L1 vaccine delivered either as VLPs or as a polynucleotide.

4. Vaccines to treat PV infection

It can be estimated that, globally, about 100 million women have already been infected with high risk genital PVs, and that about 5 million of these will have persistent infections that will in due course give rise to anogenital cancer if untreated. For this large group, there is no evidence that capsid protein based vaccines, designed to produce virus neutralising antibody, have much to offer for prevention of disease. Rather, therapy will be targeted at eliminating epithelial cells in the anogenital tract that are already infected with PV. One modality of treatment that might achieve this would be immunotherapy, either alone or in conjunction with specific antiviral drugs. Papillomaviruses generally encode six non structural proteins (termed E1, E2, E6, E7, E5, E4) and two structural proteins (L1 and L2) which are expressed differentially across the maturing epithelium, though all are present at relatively low abundance, if at all, in the self renewing stem cell populations at which immunotherapy would have to be targeted to eliminate clones of infected epithelial cells. Natural immune responses to PV encoded antigens are weak and unpredictable, with the exception of the E7 protein, to which a humoral immune response is observed in most cases of invasive cervical carcinoma. Some evidence suggests that cell mediated immune response to the E2 and E6 proteins may be predictors of regression of PV associated disease, and immune suppression in HIV infection or following transplantation is a well characterised risk factor for progression of PV infection to premalignancy and malignancy. Thus, targeting immunotherapy to some or all of these PV encoded proteins is held to have potential for treatment of PV infection. However, generally effective active immunotherapy is still a wish that has not been reduced to practice for any human disorder, despite some early successes of tumour antigen specific immunotherapy in subsets of patients with cancer. Further, there are extra problems in targeting immunotherapy to PV associated skin lesions, which lack the inflammation necessary to recruit innate immune responses.

Against this background, what has been achieved so far is to demonstrate firstly that the PV non structural proteins are adequately immunogenic, inducing responses which can be used to prevent the grafting of transplantable tumours expressing these antigens, and in some cases to cause partial regression of existing tumours. Further, in animal models, notably the cottontail rabbit papillomavirus, partial therapeutic efficacy against natural infection has been demonstrated. The optimal choice of antigen, means of production, dose, route of delivery, and frequency of immunisation has yet to be established for any animal model, though many such delivery systems have been proposed and shown of benefit in at least one animal model (P-71, P-73, P-77, P-78, P-79, P-83, P-84, P-85, P-87, P-92, P-95, P-194, P-227, O-56, O-57, O-97). In man, experiments in patients with cervical or other HPV associated cancer or precancer have demonstrated that at least some of the PV non structural proteins are immunogenic (P-89, P-91, P-98, P-99, P-100) and that there are hints of potential efficacy in a number of clinical scenarios. Major effort is required to develop surrogate markers of potential efficacy that might be used to allow cost effective dose ranging studies in man, and there is therefore great interest in the epidemiologic studies currently being undertaken, to evaluate whether viral load is predictive of clinical outcome for PV as has proven
to be the case for other viruses. Similarly, studies of cellular immune responses to vaccine proteins in man are being undertaken, though the constraint of only being able to access blood, and in limited quantity, creates practical problems which even the newer techniques of tetramer technology, ELISPOT, and intracellular cytokine staining have not yet overcome.

5. Conclusions

Vaccines to prevent PV infection, utilising PV L1 VLPs to induce neutralising antibody, are in clinical trial and show all the characteristics likely to be associated with success. Results warrant global planning for the deployment of VLP vaccines within a decade, as part of a program to prevent cervical cancer.

Vaccines designed to treat existing PV infection by inducing therapeutic cellular immunity targeted to PV proteins are at a much earlier stage of development. The wide choice of potential and proposed antigens, routes and mechanisms of delivery, and possible treatment regimens suggest that, to move the field forward, surrogate markers allowing comparison of the relative efficacy of different vaccine approaches are required. These should be based on reduction in load of virus infection, and need to be validated in animal models or in man.