COMMENTARY

HPV vaccines: Translating immunogenicity into efficacy

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ABSTRACT

Currently available human papillomavirus (HPV) vaccines are very successful at preventing persistent HPV infection and premalignant cervical lesions. In part due to the unique aspects of HPV immunogenicity and high levels of efficacy no immune correlate has been identified for HPV vaccination. Serum neutralizing antibodies are used to measure vaccine response, but their role as a correlate has not been verified, and this theory fails to explain the prevention of HPV related non-mucosal lesions. Identifying a true correlate would aid in future work in this area but will be difficult in the setting of a highly efficacious vaccine.

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Introduction

Immunogenicity is the capacity of any particular epitope to create immune response and represents the host organism's response to initial insult; either by antibody formation or cell mediated immunity via cytotoxic T lymphocytes. The immune response to natural human papillomavirus (HPV) infection is very inconsistent and is slow to develop because HPV is a relatively poor immunogen. Several factors affect HPV immunogenicity: the majority of virus replication occurs in superficial epithelial cells where the host immune system has limited access, the virus lacks an RNA intermediate avoiding the innate immune response against foreign RNA, there is little to no systemic viremia, and most encoded nucleoproteins are non-secreted.¹ While HPV viral proteins are immunogenic the innate response is slow to appear after natural infection. Antibodies to the HPV16 L1 protein develop in months to years after infection, and in some women antibodies are never identified.² Other HPV proteins such as E1, E2, or E6 create very little immune response in healthy patients; however those with cervical cancer are 14 times more likely to have an antibody response to E7, suggesting the response may only be stimulated after the onset of invasive disease.³ The cell-mediated immune response to HPV is poorly understood, but clearly plays a role given the increased rate of HPV related disease in immunocompromised patients.^{4–7} The immune response to HPV natural infection and vaccination has been well described previously, but unfortunately, no true correlate to efficacy has been identified. Current research investigating the immune correlate of HPV vaccination efficacy is reviewed here.

HPV vaccine immunogenicity

There are 3 HPV vaccines currently available in the United States and all 3 utilize virus-like-particles (VLP) composed of

the L1 major capsid protein. These are injected intramuscularly and result in a significant and sustained serum antibody response against L1.^{8–11} In addition, they are high efficacious at preventing persistent HPV infection. This high efficacy precludes definitively identifying an immune correlate for HPV vaccines, however serum neutralizing antibodies are a possible, but unlikely, immune correlate. The strongest evidence comes from animal studies in which passive transfer of antibodies to previous antibody negative animals resulted in protection from papillomavirus.^{12,13} In both rabbits and beagles the transfer of antibodies resulted in complete protection from lesions after subsequent exposure or rapid regression of minimal lesions. Importantly, these studies do not provide direct evidence of the specific role of serum antibodies in protection against papillomavirus, only that their presence was associated with protection.

In a longitudinal study of college-age women in the United States recurrent HPV infection was inversely correlated with persistent high levels of IgG antibody to HPV virus-like-particles. In addition, those subjects who had a persistent IgA response were much more likely to have elevated IgG antibodies in the serum.¹⁴ While supporting the role of antibodies, either IgG or IgA, in protection against re-infection this study also cannot provide direct evidence of the mechanism of protection.

Immunogenicity and efficacy

Identifying markers for immunogenicity, antibody or otherwise, is only part of finding an immune correlate. The marker then must be shown to correlate with or directly affect efficacy. For HPV vaccines true efficacy is not the prevention of transient or even persistent infection but the prevention of invasive cervical cancer and its precursor, high grade cervical intraepithelial neoplasia. This level of efficacy has been well documented in multiple international trials. In Brazil, 437 women

from 5 different centers were followed for 113 months after treatment with HPV-16/18 AS04-adjuvanted vaccine.⁸ All participants remained seropositive to HPV16/18 at levels higher than natural infection and it was 100% effective against cervical intraepithelial neoplasia (CIN) 2+ associated with HPV 16/18. Another study following women at centers in Brazil, Canada, and USA for 6.4 years found 100% efficacy against HPV16/18 related CIN 2+ and 12-fold high antibody concentrations when compared to natural infection.⁹

The impressive efficacy of HPV vaccines is an obvious success for women's health but presents a challenge when searching for immune correlates and it is important to recognize the relationship between efficacy and immune correlates is not always straightforward. For example, the mechanisms of immunity may be different for different stages of disease. Small pox infection is prevented by antibodies, but disseminated disease is prevented by cell mediated immunity.¹⁵ There are also cases where exposure doses can overcome immunity, both in natural infection and clinical testing. A study comparing polio vaccines found that a high enough dose of challenge virus could overcome immunity, and that higher levels of serum antibody levels in response to vaccination did not correlate with increased immunity.¹⁶ Other studies demonstrate the dose required to overcome immunity is different for naturally acquired versus induced immunity¹⁷ and that household vs. non-household sources of exposure require different levels of immunity to prevent infection.¹⁸ Some vaccines demonstrate direct correlations between immune correlates and disease, such as measles antibody titers. While high levels prevent infection and low levels do not, moderate antibody titers will prevent any clinical signs of disease despite infection occurring.¹⁹ A particularly relevant example is the study of mucosal and serum antibodies in response to influenza vaccines. Previous vaccinated subjects were challenge with virus and levels of IgG and IgA were tested. The lowest and highest infection rates were seen in those with both or neither antibodies, respectively. However, having IgG or IgA resulted in a different infection rate, indicating a synergistic relationship between serum and mucosal antibodies.²⁰

There are many different possibilities for immune correlates with HVP vaccination, including IgA antibodies, especially in the setting of a mucosal infection initiated at the cervix. When primates were immunized with HPV11 VLPs the cervical lavage obtained post-immunization did neutralize HPV11, however IgA was not detectable in cervicovaginal secretions.²¹ Some have hypothesized about the possibility of IgG transferring from the serum to the cervico-vaginal mucosa, and in women immunized with HPV16 VLPs, the presence of VLP-specific IgG was confirmed in cervical secretions.²² This finding does not account for the decrease in non-mucosal HPV lesions seen in study subjects (such as vulvar lesions), where the tissue in question is unlikely to be exposed to any serum antibodies.

A definitive immune correlate for HPV vaccination has yet to be identified and this continues to be investigated. Currently serum neutralizing antibodies are frequently used to measure sustained response to vaccination but this cannot account for the mucosal and non-mucosal efficacy of the vaccine without fully explaining an effective level of IgG antibodies at the surface epithelium or mucosal membrane. Identification of such a

correlate would serve several benefits, including evaluation of future vaccines and quantification of immunity in treated subjects. In addition, immune correlates allow for creation of vaccines where clinical trials are not ethical, and the creation of combination vaccines.²³ Given the high efficacy of current HPV vaccines additional study into the immune correlate will be very challenging, but it is still an important aspect of fully understanding and continuing to evaluate the widespread implementation of HPV vaccination programs.

Abbreviations

HPV human papillomavirus
VLP virus-like-particles

Disclosure of potential conflicts of interest

Dr. Turner has no conflicts of interest or disclosures. Dr. Huh is a consultant for Merck and THEVAX.

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