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Explanations for the high potency of HPV prophylactic vaccines

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ABSTRACT

HPV L1 virus-like particle (VLP) vaccines administered in a prime/boost series of three injections over six months have demonstrated remarkable prophylactic efficacy in clinical trials and effectiveness in national immunization programs with high rates of coverage. There is mounting evidence that the vaccines have similar efficacy and effectiveness even when administered in a single dose. The unexpected potency of one dose of these VLP vaccines may largely be attributed to structural features of the particles, which lead to the efficient generation of long-lived antigen-specific antibody-producing cells and unique features of the virus life cycle that make the HPV virions highly susceptible to antibody-mediated inhibition of infection.

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1. Introduction

The three commercial HPV prophylactic vaccines – Cervarix, Gardasil, and Gardasil-9 – are non-infectious subunit vaccines that contain virus-like particles (VLPs) of, respectively, HPV 16 and 18; HPV 6, 11, 16, and 18; and HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. The VLPs form by the self-assembly of 360 copies of the L1 major capsid protein of the virus (Fig. 1) [1]. Clinical trials that specified intramuscular injection of three vaccine doses over a six month period demonstrated high efficacy in preventing persistent incident infections and pre-malignant neoplasias induced by the HPV types targeted by the respective vaccines [2]. Vaccinees rarely tested positive for HPV infection at even a single time point, as measured by sensitive PCR assays, implying that the vaccines provide "sterilizing" immunity from initial infection in most cases. Most "breakthrough" infections in vaccinees appeared in the early months in the trials, suggesting that most of these infections represent emergence of infections preexisting at the time of vaccination, rather than new infections after vaccination [3].

There is also accumulating evidence for high effectiveness of Cervarix and Gardasil in national immunization programs [4,5]. Post hoc analyses of three clinical trials, detailed in companion articles, have provided evidence that strong protection is induced in young women even after a single dose [6–8]. In addition, surveillance studies strongly suggest that a single dose can reduce infection and neoplastic disease incidence in national immunization programs, although, as discussed in another companion article, these studies are subject to confounding biases, including differential risk for preexisting infection in single dose recipients [9,10].

The high degree of efficacy and effectiveness exhibited by the HPV vaccines, potentially even after a single dose, is exceptional for two reasons. First, no other vaccine has been successful developed against a microbe that is primarily sexually transmitted, despite considerable effort in the public and private sectors. Second, other licensed subunit vaccines are administered in a series of two or more prime/boost immunizations. It is therefore interesting to consider what factors may contribute to the unanticipated potency of the HPV vaccines. We believe that the two most important aspects are the ability of the vaccines to consistently induce high and durable titers of infection-inhibiting antibodies and an exceptional susceptibility of the virus to antibody-inhibition of infection in its target tissue. In this review, we discuss why antibodies are likely to be the prime mediators of protection, why the VLPs are exceptionally strong inducers of durable antibody responses, and why the virus life cycle makes it especially responsive to antibody-mediated inhibition. Together, these explanations provide a biologically plausible rationale for why the HPV VLPs may be the first subunit vaccine to exhibit long term effectiveness after a single dose.

2. Mechanisms of protection

Several lines of evidence support the conjectures that infection-inhibiting antibodies are the principal mediators of HPV vaccine-induced protection and that cell-mediated immune effector responses play, at best, a more limited role, although they are part of the immune response to the vaccine. First, as discussed in more

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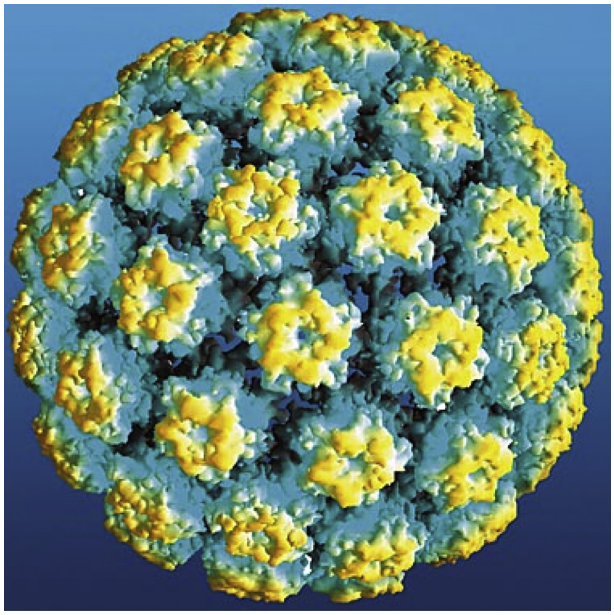

Fig. 1. Atomic model of HPV16 L1 VLP, reproduced from [54].

detail below, high and durable serum titers of VLP antibodies are consistently generated by the vaccines, and these antibodies readily neutralize the virus in *in vitro* assays. Second, antibody-mediated neutralization, like protection in the trials, is type-restricted, with the limited cross-type protection observed in clinical trials largely mirroring the antibody-mediated cross-neutralization observed *in vitro* [11]. Third, protection can be passively transferred in serum drawn from vaccinated individuals to naïve individuals in animal challenge models [12–14]. Fourth, cell-mediated effectors generally function only after infection occurs, while sterilizing immunity was observed in the clinical trials. Fifth, the vaccines had no observable effect on established infections, although such effects would be expected if cell-mediated mechanisms were primarily responsible for protection [15–17]. In this context, it is important to note that L1 is primarily a nuclear protein that is not displayed on the surface of infected cells, which makes it unlikely that L1 antibodies can induce regression of established infections/lesions by antibody-dependent cytotoxicity. Therefore, the L1 antibodies are likely to function exclusively by preventing initial events during the infection process.

However, one observation that is difficult to reconcile with an antibody effector mechanism for protection are the findings from the Cervarix phase 3 trial that protection from high grade cervical precancers (CIN3) associated with non-vaccine types appears to be stronger than protection against incident infection by the same types [18,19]. Studies of the impact of Cervarix in the Scottish immunization program support the high level of cross-protection for CIN3 observed in the clinical trial, in that the rates, irrespective of the HPV type, have decreased by more than 90% in young women who were vaccinated with Cervarix at age 13 and screened at age 20 [20]. How the vaccine could differentially induce cross-protection at the level of high grade disease is unclear.

One possible explanation for the differential protection at the level of CIN3 may be that the vaccine induces T cell responses to L1 that potentially could be cross-type protective (and there is some limited evidence to support this conjecture [21]), but that expression of L1 is normally too low in the basal epithelial cells, where productive infections are maintained (discussed below), for the infected cells to be targeted by cell-mediated responses. CIN3s are thought to arise mainly from high-risk HPV infection in a specific subset of cells in the cervical squamocolumnar junction that retain certain embryological characteristics [22]. It is possible that L1 is expressed at sufficient levels in these unusual cells to make them preferentially susceptible to type cross-protective T cell responses, thereby leading to preferential elimination of the infected cells destined to produce CIN3. Consistent with this possibility, VLP vaccination can induce regression of transplantable subcutaneous tumors that express very low levels of L1 in a mouse model [23]. The presence of an immunosuppressive microenvironment in established infections/neoplasia [24] may prevent these mechanisms from effectively functioning to induce lesion regression if the vaccines are administered in a therapeutic setting.

If antibodies are the primary mediators of protection, the question arises as to whether persistent levels of antibodies need to be maintained long term so they are present at the time of initial virus exposure or whether an anamnestic response after exposure, mediated by memory B cells, can protect from persistent infection and subsequent disease. There is precedence for the latter possibility. For example, individuals vaccinated with a hepatitis B virus (HBV) vaccine can become transiently infected, as evidenced by seroconversion for non-vaccine viral antigens, but never become symptomatic [25]. However, it is most likely that neutralizing antibodies need to be present at the time of exposure for the HPV vaccines to be most effective.

The female genital tract is generally considered to be a poor inducer of antibody responses, presumably in part to limit infertility that could result from the induction of anti-sperm antibodies [26]. In keeping with this idea, intravaginal delivery of 5 μg HPV16 VLPs, a relatively high dose, induced little if any antibody response in mice unless the tissue was chemically disrupted [27]. Although the virion antigen load that is transferred from an infected sexual partner is not well documented, it is likely to be relatively low, too low to readily induce an anamnestic response. Consistent with this conjecture, increases in VLP antibody titers, once they have stabilized after vaccination, are rare in sexually active women, although these women are fully able to mount a strong anamnestic response to an additional injected dose of the vaccine [28].

One could postulate that a breakthrough infection at a genital site with low propensity for carcinogenic progression, e.g. the vaginal wall, could induce a recall antibody response that would protect against successive rounds of auto-inoculation, which could otherwise lead to infection of the cervical transformation zone with high probability of progression. However, if this scenario occurred commonly, then vaccination of women with prevalent infection would be expected to have a reduced rate of progression to high grade precancer, but this type of protection was not observed in the clinical trials [15,17].

Although 40% of vaccine recipients in the Gardasil trials were reported to become seronegative for HPV18 by four years post-vaccination, there was no evidence that Gardasil was less protective against HPV18 infection than against infection by the other three types targeted by the vaccine, for which a higher percentage of subjects remained seropositive. This observation prompted the proposal that perhaps memory B cells are sufficient to serve as effectors of protection [29]. However, this explanation no longer needs to be invoked, as the apparently lower immunogenicity of the HPV18 VLPs in Gardasil is primarily an artifact of the performance of the serological assay used in the clinical trials. For each of the four HPV types targeted by the vaccine, the assay that Merck used measured the ability of the serum polyclonal antibodies induced by vaccination to compete with a type-specific monoclonal antibody for VLP binding. The binding site of the HPV18 monoclonal antibody they used appears to overlap less consistently with the immunodominant epitopes recognized by the sera

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