Immune responses to human papilloma viruses

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Received February 16, 2009

HPV infection in the genital tract is common in young sexually active individuals, the majority of whom clear the infection without overt clinical disease. However most of those who develop benign lesions eventually mount an effective cell mediated immune response and the lesions regress. Regression of ano-genital warts is accompanied histologically by a CD4+ T cell dominated Th1 response; animal models support this and provide evidence that the response is modulated by CD4+ T cell dependent mechanisms. Failure to develop effective CMI to clear or control infection results in persistent infection and, in the case of the oncogenic HPVs, an increased probability of progression to CIN3 and invasive carcinoma. The central importance of the CD4+ T cell population in the control of HPV infection is shown by the increased prevalence of HPV infections and HGSIL in individuals immunosuppressed as a consequence of HIV infection. The prolonged duration of infection associated with HPV seems to be associated with effective evasion of innate immunity as reflected in the absence of inflammation during virus replication, assembly and release, and down regulation of interferon secretion and response thus delaying the activation of adaptive immunity. Serum neutralising antibody to the major capsid protein L1 usually develops after the induction of successful cell mediated immunity and these antibody and cell mediated responses are protective against subsequent viral challenge in natural infections in animals. Prophylactic vaccines consisting of HPV L1 VLPs generate high anti L1 serum neutralizing antibody concentrations and in clinical trials have shown greater than 95 per cent efficacy against both benign and neoplastic genital HPV associated disease. These vaccines are delivered intramuscularly and therefore circumvent the immune evasion strategies of the virus.

Key words Antibody - cell mediated immunity - human papillomavirus - prophylactic vaccine - VLPs

Introduction

From the standpoint of the evolutionary microbiologist, papillomaviruses are very successful infectious agents. They induce chronic infections that have no apparent systemic sequellae and rarely kill the host, but periodically shed large amounts of infectious virus for transmission to naïve individuals. To achieve this successful lifestyle, HPVs must either avoid or negotiate the powerful immune defence systems of the host. Host defence is a partnership between innate immunity (phagocytes, soluble proteins e.g., cytokines, complement and epithelial barriers) together with adaptive immunity (antibody, cytotoxic effector cells). In simple terms, the innate immune system detects the pathogen and acts as first line defence clearing (it is estimated) up to 90 per cent of microbial assaults alone¹. Innate immunity has no specific memory but crucially activates the appropriate adaptive immune response
that generates both lethal effector responses of exquisite specificity for, and long lived-cells with, memory for the insult. Thus, the adaptive responses of antibody mediated humoral immunity clear free virus particles from body fluids and can prevent re-infection by virus, those of cell mediated immune (CMI) responses are essential for the clearance of virus infected cells. Innate immunity is alerted by cell injury and stress or cell death, phenomena that activate the innate sensors such as Toll like receptors and the inflammasome and manifested by inflammation (the local vascular response to injury).

In the inflammatory process soluble and cellular innate immune effectors are recruited and local parenchymal cells and phagocytes (both recruited and local) are activated to secrete inflammatory cytokines and other defence molecules that in turn recruit more cytotoxic effectors to the inflammatory focus. Crucially dendritic cells in the periphery are activated to kick start the adaptive immune response by presenting antigen to naïve T cells in the draining lymph node. How this marvelous defence system is recruited to respond to HPV infections and how the virus ducks and weaves to avoid it is the subject of this brief review.

**HPVs are exclusively intra-epithelial**

The exclusively intra-epithelial life cycle of HPVs is central to understanding the host response. Virus infects basal keratinocytes probably via micro-abrasions of the epithelial surface that leave the basal lamina intact. All subsequent events in the viral life cycle are tightly linked to the differentiation programme of the keratinocyte as it progresses up through the epithelium. The terminal events that result in genome encapsidation, viral assembly and maturation of infectious virus occur in the most superficial differentiated cells of squamous epithelium. This intra-epithelial life cycle has some key features that impact on the recognition and response of the host immune system to papillomaviruses. Firstly no inflammation accompanies viral infection and thus there is no danger signal to alert the innate immune sensors. HPVs are not lytic viruses the life cycle is played out in the keratinocyte a cell destined for death from natural causes and high level viral replication and viral assembly occur in terminally differentiated keratinocytes, cells that have already undergone a regulated death programme. Secondly, although HPVs appear to be able to bind to and enter cells other than keratinocytes, viral gene expression and viral protein synthesis are confined to keratinocytes. There is no synthesis of viral protein in antigen presenting cells. Finally there is either no or very little viraemia. Virus infects via microabrasions that leave the basal lamina intact and is shed from mucosal or cutaneous surfaces far from vascular channels. Thus, there is poor access to the draining lymph nodes where adaptive immune responses are initiated.

**Immune responses to HPV**

**Regressing genital warts**

In view of these impediments, one might well ask whether there is an immune response to HPV but evidence from a range of sources shows that there is. Spontaneous regression is a feature of both cutaneous and ano-genital warts and immunohistological analysis of this phenomenon is informative. Non-regressing genital warts are characterised by a lack of immune cells, the few intra-epithelial lymphocytes present are CD8 T cells and mononuclear cells are present mainly in the stroma. Histological examination of regressing genital warts reveals a large infiltrate into the wart stroma and epithelium of T cells (both CD4+ and CD8+) and macrophages. The infiltrating lymphocytes express activation markers, the cytokine milieu is dominated by pro-inflammatory cytokines such as IL-12, TNF-α and IFN-γ and there is upregulation of the adhesion molecules required for lymphocyte trafficking on the endothelium of the wart capillaries. These appearances are characteristic of a cell mediated Th1 biased immune response.

**Natural animal infections**

Cross sectional clinical studies provide only a snapshot of what is a dynamic process and ethical and practical considerations inhibit longitudinal studies in humans. However, in animal models of mucosal papillomavirus infection such as the canine oral papillomavirus (COPV) the immunological events of the entire wart cycle from infection to regression can be followed. In COPV infections wart regression is accompanied by a cellular infiltrate similar to that seen in regressing cutaneous and genital warts. Systemic T cell responses directed to E2 and E6 peptides can be detected at low frequency at distinct time points during the infectious cycle. These responses occur in narrow time windows that coincide with periods of viral DNA amplification and are maximal at the time of wart regression thereafter declining quite rapidly. Serum neutralising antibody to the major capsid protein L1 can be detected at or just after wart regression (Fig. 1) with peak titres 2-3 wk post wart clearance. Serum antibody concentrations even at peak are modest and
slowly decline in the following weeks and months but animals remain resistant to challenge with large doses of infectious virus even in the absence of detectable serum antibody.

**Epidemiological and natural history studies**

Epidemiological and natural history studies strongly suggest that the course of events in HPV infections follow a similar pattern (Fig. 2). Virtually all natural history studies show that genital HPV infection (as determined by detection of HPV DNA in cervico-vaginal lavages) is extremely common in young sexually active women with a cumulative prevalence of 60-80 per cent. Most of these HPV infections “clear” i.e., DNA for that specific HPV type can no longer be detected. The time taken to clearance for the hrHPVs particularly HPV 16 seems on average to be 8-16 months, considerably longer than the 4-8 months reported for the low risk HPVs. However if the immune response fails to clear or control the infection then a persistent infection, often with focally high levels of hrHPV DNA is established and it is this cohort of individuals that have an increased probability of progression to high grade cervical intra-epithelial neoplasia (CIN 2/3) and invasive carcinoma.

**Cell mediated immunity to HPV**

The increased incidence and progression of HPV infections in immunosuppressed individuals illustrates the critical importance of the CD4 T cell regulated cell mediated immune response in the resolution and control of HPV infections. HIV infected patients show multiple recurrences of cervical HPV infections and an increased incidence of both of cutaneous and genital warts that appears to reflect an increased risk of progression from sub clinical to clinical disease. Prospective studies show prolonged persistence of hrHPV DNA in HIV infected 13-18 yr old girls who are otherwise healthy and a high incidence of CIN2/3 in this group. Importantly the risk for incident CIN in these HIV infected girls appeared to be due primarily to the persistence of low grade squamous intra-epithelial neoplasia (LSIL), rather than the persistence of hrHPV DNA without a detectable lesion, implying that florid...
viral gene expression in a persistent active infectious cycle is important in progression.22

**CD4 T cell responses**

There is increasing evidence that, as in COPV, CD4 T cell responses to E2 and, probably E6 are important at least in hrHPV infections. A non intervention follow up study of women with cytological evidence of low grade CIN, showed that HPV16 E2-specific T cell responses, as measured by specific IL-2 release in vitro, occurred frequently at the time of lesion clearance23. Good Th1 type immunity against the E2 and E6 protein has been detected in healthy individuals with no clinical signs of HPV16 infection24. Importantly, these Th1 type responses were found only occasionally in high-grade CIN patients and were impaired in cervical cancer patients25. In a longitudinal study extending over 12 months of women with histologically diagnosed CIN 1 systemic CD4+ responses to E2 were detected in HPV 16+ histological regressors but were absent in HPV 16+ histological progressors. No E2 specific responses were found in patients with high grade CIN2/3 at the time of recruitment (Woo, van der Burg and Stanley, unpublished observations). These data suggest that a hallmark of effective immune control of HPV 16 infection in the cervix is the generation of CD4+ cells specific for E2.

**Cytotoxic effectors**

Cell mediated cytotoxicity is the most important effector mechanism for the control and clearance of viral infections and is implemented by a range of cells both antigen specific cytotoxic T cells (CTL) and the so called “innate lymphocytes” a heterogeneous group that includes natural killer (NK) cells, γδ T cells and invariant natural killer T cells (iNKT). HPV specific CTL can be detected in patients with previous26 or ongoing HPV infection27-29. Both CD4+ and CD8+ cytotoxic effectors have been shown to be involved in these responses30. In a longitudinal study of women with PCR determined cervical HPV 16 infection lack of CTL response to E6 but not E7 correlated with persistent HPV infection suggesting that a CTL response to HPV 16 E6 is important for viral clearance and, by implication, neoplastic progression31.

NK cells are key components of the innate immune response to viral infections. They are a sub-set of lymphocytes that kill virally infected or tumour cells lacking surface expression of MHC Class I molecules and there is evidence that they are important in HPV infections. Abnormal NK cell function correlated with more frequent recurrence of disease in children with RRP32. A subset of patients with severe combined immunodeficiency followed up over the long term post haemopoietic stem cell transplantation33 exhibited severe cutaneous papillomatosis associated with either common γc receptor cytokine subunit or Janus kinase-3 (JAK-3) deficiency. A common consequence of such signalling defects is natural killer cell deficiency and indeed NK cell counts were lower in these patients. PBMC from patients with active HPV 16 neoplastic disease display a reduced NK cell activity against HPV 16 infected keratinocytes34,35. Large numbers of γδ T cells migrate into regressing papillomas induced by BPV36 but there are no published data showing that these cells form a significant infiltrate in regressing HPV induced lesions37.

**Humoral immune responses**

Numerous serological studies using HPV virus like particles (VLPs) have shown that infection with a genital HPV is followed eventually by sero-conversion and type specific antibody to the major viral coat protein L1; antibody to the minor viral coat protein L2 is not detectable in natural infections in animals or humans38. Sero-conversion most frequently occurs between 6 and 18 months after the first detection of HPV DNA in subjects with persistent HPV infection i.e. detection of HPV DNA of the same type on two occasions at least 6 months apart39-41 and rarely in subjects with incident HPV infections i.e., detection of HPV DNA on only one occasion42. However, as in animal infections, antibody concentrations are low even at the time of sero-conversion. Furthermore not all HPV infected subjects sero-convert and 20-50 percent of women with HPV DNA do not have detectable type specific anti- HPV antibodies although this statement must be qualified by the fact that the current serological assays are relatively insensitive41,43. The modest humoral response is not surprising since there is no blood born
phase of infection and free virus particles are shed from the surface of squamous epithelia with poor access to vascular and lymphatic channels and hence to lymph nodes where immune responses are initiated. Anti-HPV L1 antibodies however persist for many years and 10 years post the first detection of HPV DNA approximately 20-25 per cent of women remain antibody positive. A controversial issue is whether these low levels of anti-L1 antibody protect against re-infection with the same HPV type. This question is not easy to address. There is increasing evidence that HPV is not cleared when lesions regress but as in COPV, CRPV and BPV infection remains in a latent state in a few basal keratinocytes. The detection of HPV DNA of the same type in a sero-positive individual may therefore reflect reactivation of latent virus rather than re-infection. Only if the “new” HPV DNA can be shown to be distinct in sequence from the HPV DNA originally detected can re-infection be proven.

**HPV avoids host defences**

Why HPV infection remains ignored or undetected by the immune system for so long is a central question. HPV infections are exclusively intra-epithelial and, theoretically, HPV attack should be detected by the professional APC of squamous epithelia, the Langerhans cell (LC). The activated LC should then migrate to the draining lymph node, processing HPV antigens en route, present antigen to naive T cells in the node that then differentiate into armed effector cells, migrate back to the infected site and destroy the infected keratinocytes.

This cycle of events is deflected in a number of ways. The infectious cycle of HPV is in itself an immune evasion mechanism inhibiting host detection of virus. HPV replication and release does not cause cell death since the differentiating keratinocyte is already programmed to die and this “death by natural causes” does not act as a danger signal in the infected site. Thus, for most of the duration of the HPV infectious cycle there is little or no release into the local milieu of pro-inflammatory cytokines important for dendritic cell activation and migration and the essential signals to kick start the immune response in squamous epithelia are absent. However, even in the absence of viral induced cytolysis and cell death, HPV infected keratinocytes should be activated to induce type 1 interferon responses - a powerful, generic, anti-viral, defence system. The type 1 interferons, IFN-α and IFN-β, have antiviral, antiproliferative anti-angiogenic and immunostimulatory properties acting as a bridge between innate and adaptive immunity activating immature DC. Most DNA viruses have mechanisms for inhibiting interferon synthesis and signalling and the papillomaviruses are no exception.

High risk HPV infection downregulates IFN-α inducible gene expression and the HPV16, E6 and E7 oncoproteins directly interact with components of the interferon signalling pathways (see 59). Thus, E7 inhibits IFN-α mediated signal transduction by a binding to P48/IRF-9 preventing translocation to the nucleus, thereby inhibiting the formation of the ISGF-3 transcription complex that binds ISRE (interferon specific response element) in the nucleus. E7 inhibits IFN-β and MCP-1 by inhibition of the transactivating function of IRF-1. E7 interferes with intermediate IFN mediated signals also by physically associating with IRF-1 inhibiting IRF-1 mediated activation of the interferon-β promoter recruiting histone deacetylase to the promoter, thereby preventing transcription. In vivo expression of HPV18 E7 results in reduced expression of IRF-1 target gene such as TAP1, IFN-β and MCP-1 by inhibition of the transactivating function of IRF-1. The E6 protein of HPV also targets the interferon pathway. E6 binds to IRF-3 and inhibits its transcript activation function thereby preventing transcription of IFN-α messenger RNA. E6 binds to TYK2 preventing binding to the

**Virus capsid entry is usually an activating signal**

for dendritic cells but there is evidence that Langerhans cells are not activated by the uptake of HPV capsids. Langerhans cells, when incubated with L1 virus like particles (VLPs) of HPV16 do not initiate epitope specific immune responses against L1 derived antigens. In contrast, stromal dendritic cells are activated by VLP and stimulate HPV specific T cells. Studies in TLR 4 (Toll like receptor) deficient mice suggests that TLR4 contributes to the recognition of HPV16 VLP by stromal DC.

**Interference with Interferon**

For most of the duration of the HPV infectious cycle there is little or no release into the local milieu of pro-inflammatory cytokines important for dendritic cell activation and migration and the central signals to kick start the immune response in squamous epithelia are absent. However, even in the absence of viral induced cytolysis and cell death, HPV infected keratinocytes should be activated to induce type 1 interferon responses - a powerful, generic, anti-viral, defence system. The type 1 interferons, IFN-α and IFN-β, have antiviral, antiproliferative anti-angiogenic and immunostimulatory properties acting as a bridge between innate and adaptive immunity activating immature DC. Most DNA viruses have mechanisms for inhibiting interferon synthesis and signalling and the papillomaviruses are no exception.

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cytoplasmic portion of the IFN receptor inhibiting phosphorylation of TYK2, STAT1, STAT2 impairing JAK STAT activation and therefore inhibiting specifically IFN-α mediated signalling. DNA microarray analysis of gene expression shows that HPV16 alters expression of 3 groups of genes, interferon response genes, NF-κB stimulated genes and cell cycle regulation genes. E6 decreases expression of IFN-α and β, downregulates nuclear STAT-1 protein and decreases binding of STAT1 to the ISRE. E6 and E7 therefore directly alter expression of genes that enable host resistance to infection and immune function.

One can conclude that HPV efficiently evades the innate immune response and delays the activation of the adaptive immune response but eventually the defences are activated the infection is controlled and immune memory to that specific HPV type is established. There are risks to the host of such a strategy since the host DC’s are exposed to low levels of viral proteins in a non-inflammatory milieu for a protracted time period and local immune non-responsiveness may be established in the infected mucosa. In this milieu that is operationally HPV antigen tolerant, host defences could become irrevocably compromised, HPV antigen specific effector cells may either not be recruited to the infected focus or their activity could be down regulated or both. Thus, if during a persistent high risk HPV (hrHPV) infection there is deregulation of hrHPV E6 and E7 with increased protein expression this might not result in an armed effector CMI response but rather the dominance of T regulatory cells. In consequence, progression to high grade CIN and invasive carcinoma would not be impeded.

**Prophylactic HPV vaccines**

It might well have been thought that since the antibody response in natural infections was so modest that vaccines that generate serum neutralizing antibodies would not be effective. However, some of the earliest experimental work in rabbits using CRPV, showed very clearly that neutralizing antibodies were protective. In these experiments, if rabbits were infected systematically with CRPV by direct injection of virus into the muscle or bloodstream, papillomas did not arise on the skin of the challenged animals, but neutralizing antibodies were generated and the animals were completely resistant to viral challenge by abrasion of the epithelium. This and other data suggested very strongly that generating neutralizing antibodies to virus capsid proteins would be an effective prophylactic vaccine strategy and this has proved to be so. Two HPV L1 VLP vaccines have been developed: Cervarix®, a bivalent HPV 16, 18 VLP vaccine from GlaxoSmithKline and Gardasil® also known as Silgard, a quadrivalent HPV 16/18/6/11 vaccine from Merck Vaccines. These products are to be delivered in a 3 shot immunisation schedule and induce, at their peak after the third immunisation at 6 months, high concentrations of neutralizing antibodies to L1 and virtually all subjects in the vaccine trials have seroconverted. These vaccines are delivered intramuscularly, resulting in rapid access of antigen to the local lymph nodes, thus circumventing the immune avoidance strategies of the viral intraepithelial infectious cycle. Furthermore, HPV L1 VLPs are highly immunogenic, inducing potent antibody responses in the absence of adjuvant due to their ability to activate both innate and adaptive immune responses. VLPs are rapidly bound by myeloid DCs and B lymphocytes, and signal via the toll-like receptor dependent pathway which is essential for B cell activation and antibody generation in mice and probably also in humans.

The currently available vaccines have been shown to be highly efficacious in the various Phase II and Phase III randomized control trials (RCTs) achieving over a 5 year period 100 per cent protection against HPV 16/18 caused high grade cervical intra-epithelial disease (CIN2/3) in 15-26 year old women naïve for HPV 16 and/or 18 at trial entry. Currently, the best assumption is that the mechanism of protection elicited by VLPs is serum antibodies. The most unequivocal evidence for this notion comes from experiments in rabbits and dogs in which it was shown that naïve animals passively immunized with purified serum IgG from either VLP immunized or naturally infected animals were completely protected against high viral challenge. The mechanism by which neutralizing antibodies to HPV prevent viral entry is at present speculative. However, new data on virus entry to cells suggest different stages at which neutralizing antibodies could be effective. Recent studies have shown that HPV infection requires a micro abrasion of the squamous epithelium that results in epithelial denudation but retention of the epithelial basement membrane. HPV initially binds by a primary receptor to this exposed basement membrane before entering the keratinocyte, presumably as the keratinocyte migrates along the basement membrane to repair the small wound. This is a protracted process extending over 24 to 48 h, during which it is speculated the virus capsid undergoes conformational changes that expose the secondary receptor by which the virus binds to and
enters the keratinocyte. Virus neutralizing antibodies could act therefore, by binding to the receptors or by binding to the capsid and preventing the conformational distortion essential for successful viral entry. Probably both types of antibodies are generated after VLP immunization, but in general, higher concentrations of blocking antibodies (anti-receptors) are needed for neutralization compared with those preventing conformational changes. This is of interest since it implies that relatively low concentrations of the latter would be needed for protection and is consistent with observations from animal papillomavirus studies. For example, in the dog and rabbit low concentrations of anti L1 antibodies provide long-term protection against high doses of challenge virus. Detectable anti L1 antibody persists in vaccinated subjects at least over 5 years in most vaccinees but HPV 18 antibody concentrations fall to background levels in about 20 per cent of subjects immunised with the quadrivalent vaccine. However, efficacy against HPV 18 associated CIN2/3, AIS and VIN/ValN3 remains at 100 per cent over a 4 year period irrespective of antibody level and attack rates of HPV 18 in the placebo group remain constant over this time (Ault 2007, personal communication).

Mathematical modelling of the kinetics of antibody decay indicates that antibody (at least for yeast derived HPV 16 VLPs) could persist for 30 years and crucially there is good evidence that robust immune memory is generated by these vaccines. The quadrivalent vaccine has shown an impressive recall response to antigen challenge, the functional read out for memory, 5 years post immunisation and circulating B memory cells can be detected 1 month after the third and final immunisation with the bivalent vaccine. Furthermore, the persistence of antibody levels in excess of that found in natural infection strongly suggests robust B and T memory induction. Immune memory is fundamental to successful immunisation and the observations of persistence of antibody and robust recall from the VLPs in the trials leads to optimism that the duration of protection might be measured in decades as for example has been shown for in hepatitis B sub unit vaccines.

Cross protection

In natural HPV infections, the detectable neutralizing antibody responses are type specific, but HPV L1 VLP vaccines generate not only type specific but cross-reactive and cross-neutralizing antibodies. Both commercial prophylactic vaccines have now shown evidence of cross-protection, or protection against non-vaccine HPV types. The high antibody concentrations generated by the vaccines probably explain this phenomenon. In general, the population of antibodies produced in response to a particular antigenic stimulus such as a VLP, is heterogeneous. Most antigens are structurally complex, containing many different epitopes or antigenic determinants. The immune system responds to the antigen by producing antibodies to most of the accessible epitopes. Thus, in any response to a specific protein there will be several populations of antibodies; the overall antibody response is polyclonal or heterogeneous and it comprises the output of all the individuals’ stimulated B cells. Epitopes recognized by B cells are usually a confirmation and these B cell epitopes are only displayed by proteins in the native or tertiary structure. Complex proteins such as L1 contain multiple overlapping epitopes, some of which are immunodominant, that is, they induce a more profound and stronger response in the host than other epitopes and therefore dominate the polyclonal response. This can be seen quite clearly in the antibody response to HPV L1 VLPs. The immunodominant antibodies are type-specific antibodies but there are, subpopulations of other antibodies, some of which will be to epitopes shared by other HPV types. In natural infections, the antibody concentrations generated are low so that only the immunodominant species is detected, but in VLP immunized individuals, antibody concentrations are high and the subpopulations of cross-reactive and cross-neutralizing can therefore be detected in sero assays. These subpopulations are present at antibody concentrations one to two logs lower than the dominant type-specific neutralizing antibodies. Not every individual will generate cross-neutralizing antibodies since immunodominance is complex.

Summary

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References
is mediated by Fc\(_\gamma\) receptors and contributes to acquisition of T cell immunity. J Immunol 2007; 178 : 7587-97.


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