Virology 384 (2009) 410–414

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

Minireview

Interaction of human papillomaviruses with the host immune system: A well evolved relationship

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ARTICLE INFO

Article history:
Received 24 September 2008
Accepted 3 October 2008
Available online 4 November 2008

Keywords:
Papillomaviruses
Humoral immunity
Cellular immunity
Vaccines

ABSTRACT

Human papillomavirus (HPV) infections are generally long lasting, and a host immune response to infection is hard to detect. Nevertheless immunocompromised subjects control HPV infection less well than those with intact immunity. Immune responses are best documented for the papillomavirus groups that cause evident human disease, particularly those responsible for anogenital cancers and genital warts. Humoral immunity to the viral capsid has been shown sufficient for protection against infection, while innate and adaptive cell mediated immunity appears important for eventual elimination of HPV infection. However, molecular and cellular mechanisms responsible for protection from and clearance of HPV infection are not completely established.

Host virus interactions: a primer

Viruses evolve to maximise reproductive fitness in their host (Marques and Carthew, 2007). Given time, mammalian viruses and their host reach a state of equilibrium where the host is not greatly disadvantaged in its reproductive capacity by virus infection, and the virus is not too limited in reproductive capacity by the host immune response. Papillomaviruses and their adapted mammalian hosts appear to have reached that state of equilibrium over many generations (Bernard, 2005). This paper will examine the mechanisms used by papillomaviruses, and the host, to maintain that equilibrium.

Mammals have evolved sophisticated innate and adaptive immune mechanisms to control local and systemic viral infection, and to limit damage to the host where infection persists. Despite these mechanisms, most papillomavirus infections are relatively long lasting. How do papillomaviruses evade induction of host protective immune responses? Triggering of innate immune mechanisms is a key initiator of both innate and adaptive immune effector mechanisms for viral clearance. Triggers include double stranded RNAs, single stranded DNAs, bacterial cell membrane components, intracellular molecules released following unprogrammed cell death, and cell membrane associated molecules displayed by distressed cells. Papillomaviruses are double stranded DNA viruses that undergo their vegetative reproductive cycle within, and in synchrony with, squamous epithelial cells (Doorbar, 2005). They exit from mature epithelial cells already programmed to undergo apoptosis, and are shed to the environment. Thus, of the triggers to initiate an immune response, only expression of membrane associated stress molecules (Strid et al., 2008; Textor et al., 2008) would likely occur as a consequence of disturbed cell cycle control. Further, negative regulation of adaptive immunity is initiated by persisting presentation of PV antigen in epithelium (Doan et al., 2000) in the absence of innate immune stimuli. Thus, the opportunity for papillomavirus infection to induce specific immune mechanisms is limited.

Immune mechanisms controlling HPV infection

There are few data on the host immune interaction with the many papillomaviruses not associated with evident disease. Their pathogenic potential does not appear to be enhanced by immune deficiency, though in immunosuppressed subjects some of the "non-pathogenic" HPVs may be more easily detected in apparently normal skin suggesting higher viral copy numbers, while other are associated with immunodeficiency associated squamous cancers (Berkhout et al., 2000; Asgari et al., 2008). Papillomaviruses commonly associated with human disease are arguably less well adapted to their mammalian host. There is a particular interest in the PVs designated high risk, belonging to the clades (Chan et al., 1995) predisposing to cancer of the skin (β1) and of the genital tract (α7,9). Study of the immune response to these viruses is made difficult by PV specificity for a single host species, and by the limited range of systems for studying viral reproduction *in vitro*. A successfully resolved prior infection with HPV appears to protect against further infection with that HPV type. Vaccines recently developed to prevent HPV16 and HPV18 associated anogenital cancer consequent of persisting HPV infection induce humoral immune responses to conformational epitopes on the HPV16 and HPV18 viral capsid that are sufficient to provide long lasting protection against viral challenge (Kahn and Burk, 2007b). However, the lower titre humoral immune responses to viral capsids

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0042-6822/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.virol.2008.10.004

induced by natural HPV infection are neither particularly strong nor particularly long lasting (Carter et al., 2000), do not correlate well with detection of HPV DNA (Andersson et al., 2008), and their role in prevention of further HPV infection is uncertain, particularly as antibody may not be necessary to provide protection against re-infection. Although there are immunodeficiency syndromes in which persistent warts are associated with hypogammaglobulinemia, these patients always have impaired cellular immunity in addition (Hamblin, 2007; Diaz and Gulino, 2005; Lawrence et al., 2005a; Reid et al., 1976; Wilson et al., 1976); whereas, children with simple agammaglobulinemia both anecdotally and from the lack of published literature appear to be no more prone than immunocompetent children to recurrent HPV associated skin or genital warts. In contrast, subjects with persistent cell mediated immune defects, whether due to HIV infection (Palefsky, 2007), persistent iatrogenic immunosuppression as therapy for autoimmune disease or renal transplantation (Paternoster et al., 2008; Ulrich et al., 2008), or congenital partial cellular deficiencies (Lawrence et al., 2005b; Bernier-Buzzanga and Su, 1990) all are at increased risk of persistence of infection with and disease caused by pathogenic papillomaviruses, and associated cancers of the skin and the anogenital tract. Interestingly individuals with compromised cellular immunity do not appear to be at risk of new infection with the common childhood wart virus infections, suggesting that the memory response protecting against reinfection, whether antibody or cell mediated, may not use the same components of the adaptive immune system as the effector response necessary to control persisting latent or vegetative infection. While impaired cellular immunity hinders clearance of HPV infection, the 2% of infections with high risk HPV that persist do so in apparently immunocompetent individuals. There is nevertheless a substantial heritable component to cervical cancer risk (Hemminki and Chen, 2006). Some genetic determinants of risk of persisting HPV infection are defined (Garcia-Pineres et al., 2006) and these may include polymorphisms in genes controlling the nature of effector T cell responses (Morahan et al., 2002), as has been shown for other persistent viral infections (Yilmaz et al., 2007; Hegazy et al., 2008).

The role of innate immune mechanisms in controlling HPV infection is difficult to determine from natural history studies, as most innate immune mechanisms are necessary for embryogenesis or host survival, and those that are not do not appear associated with an increased risk of development of, or persistence of, skin or genital warts. An exception is WHIM syndrome, characterised by absence of the chemokine receptor CXCR4 and associated with poor neutrophil trafficking and persistent cutaneous warts (Gulino, 2003), suggesting a role for polymorphonuclear phagocytes in clearance of HPV infection. Involvement of other innate immune mechanisms, such as IFN release from NK cells, in control of HPV infection can however be inferred from mechanisms developed by papillomaviruses to evade them (Lee et al., 2001).

Measured immune responses to HPV infections

Viral capsid proteins

The most immunogenic component of pathogenic papillomaviruses is the major capsid protein, L1, assembled as 72 pentamers into a virion. Binding of antibody to the viral capsid can be measured by ELISA (Christensen et al., 1994) using virus like particles as substrate, or by inhibition of binding of a labelled monoclonal antibody specific to a capsid determinant (Opalka et al., 2003). Capacity for viral neutralisation can be assessed *in vivo* using purified virions and susceptible target cells (Christensen and Kreider, 1990), or *in vitro* using pseudovirions encoding a reporter gene expressible in a susceptible target cell (Roden et al., 1996). Infection with a pathogenic papillomavirus produces a humoral immune response to the virus capsid which recognises predominantly conformational determinants displayed only when the L1 protein is correctly configured into pentamers as in the native virus (Christensen et al., 1994). The adaptive immune response to HPV is slower to appear than that to most pathogenic virus infections (Carter et al., 2000). Antibody titres following natural infection are low, and assays are difficult to standardize (Ferguson et al., 2005). For the well studied genital papillomaviruses (HPV 6,11, 16, and 18), mean times to seroconversion exceed 6 months, and 30–50% of individuals with evidence of persisting genital HPV infection appear never to acquire antibody (Carter et al., 2000). After clearance of viral infection, viral capsid antibody titres fall. Nevertheless, about 50% of HPV16 seropositive, HPV16 DNA −ve individuals will retain antibody over 5–7 years (Wang et al., 2004). Clearance of antibody after infection is not well documented for other virus types. Where infections persist, antibody also appears to persist, and patients with cancers arising from high risk genital HPV infections can have measurable viral capsid antibody titres many years after the infection that triggered the cancer, though seropositivity for the cancer HPV type in patients with cancer is generally reported at between 30% and 50% (Carter et al., 2001). Antibody to the common skin papillomaviruses (HPV 1 and 2) is found in 30% to 50% of children with warts, and with similar frequency in unselected teenage children (Carter et al., 1993; Cubie et al., 1998). Antibody to the viral capsid of the PVs causing cancer in the skin of immunosuppressed patients (HPV5 and 8) however appears to be rare in a healthy population (Favre et al., 1998). Thus, capsid antibody is likely a measure of persisting HPV infection, though many with infection do not have antibody, and disease site, viral load or local inflammation may determine the extent to which antibody is produced. CD4+ T cell responses to capsid protein, necessary for optimal antibody and cytotoxic T cell production, are also reported following genital HPV infection, and are more evident in disease infiltrating lymphocytes in the cervix than in the blood (Passmore et al., 2006; Williams et al., 2002). The minor capsid protein L2 is immunogenic during natural infection (Viladiu et al., 1997; Kanda et al., 1995) though antibody to L2 within a virion after natural infection has been hard to detect, perhaps because the relevant epitopes are only displayed after virion binding to the cell surface (Day et al., 2008b).

Thus, capsid specific immune responses are of limited diagnostic utility and seem unrelated to the process of viral clearance.

Viral non-structural proteins

Humoral immune responses to the 6 PV non-structural proteins commonly expressed in disease associated human infection (E1, E2, E4, E5, E6, and E7) have generally been measured using recombinant fusion proteins or linear peptides. The most consistent response is seen in patients with cervical cancer associated with HPV16 infection, who display antibody to the E7 protein (Jochmus-Kudielka et al., 1989),most commonly with invasive and metastatic disease. Healthy adults and patients with HPV 16 associated cervical intraepithelial neoplasia (CIN) demonstrate positive skin test reactions, a measure of cellular immunity, to E2, E6 and E7 peptides (van den et al., 2008). Cellular immune responses are also evident in clinical disease as infiltrates within lesions (van et al., 2008), though the proportion of T cells in infiltrates specific for PV non-structural antigen is unknown. At the time of genital wart regression, substantial mononuclear and other cellular infiltrates can be demonstrated (Coleman et al., 1994). Papillomavirus associated precancer lesions of the cervix (CIN 2/3) have substantial T cell infiltrates whether disease regression appears likely or not, as they are equally present in HIV+ve and HIV−ve individuals (Kobayashi et al., 2002). Similar infiltrates are found in cervical cancer, and the ratio of CD4 to CD8 T cells appears to fall as HPV associated lesions progress towards cancer (Monnier-Benoit et al., 2006). CD4 cellular immune responses to two viral non-structural proteins, E2 and E6, promote regression of warts caused by canine oral papillomavirus (Jain et al., 2006). Similarly, CD4 T cell responses to HPV16 E2 and E6 are measurable in some patients with regressing cervical disease and are not seen in persistent infection (de et al., 2002;