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Review

Evasion of host immune defenses by human papillomavirus

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ABSTRACT

A majority of human papillomavirus (HPV) infections are asymptomatic and self-resolving in the absence of medical interventions. Various innate and adaptive immune responses, as well as physical barriers, have been implicated in controlling early HPV infections. However, if HPV overcomes these host immune defenses and establishes persistence in basal keratinocytes, it becomes very difficult for the host to eliminate the infection. The HPV oncoproteins E5, E6, and E7 are important in regulating host immune responses. These oncoproteins dysregulate gene expression, protein–protein interactions, posttranslational modifications, and cellular trafficking of critical host immune modulators. In addition to the HPV oncoproteins, sequence variation and dinucleotide depletion in papillomavirus genomes has been suggested as an alternative strategy for evasion of host immune defenses. Since anti-HPV host immune responses are also considered to be important for antitumor immunity, immune dysregulation by HPV during virus persistence may contribute to immune suppression essential for HPV-associated cancer progression. Here, we discuss cellular pathways dysregulated by HPV that allow the virus to evade various host immune defenses.

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1. Introduction

Papillomaviruses (PV) are small DNA viruses that have coevolved for millions of years with various host species, including mammals, reptiles, and birds (Van Doorslaer, 2013). As of now, over 300 PV genotypes have been discovered. Human papillomavirus (HPV) infects mucosal and/or cutaneous skin and causes benign or malignant tumors. Defined as group 1 or 2 carcinogens by the International Agency for Research on Cancer (IARC), ~25 high-risk HPV genotypes are causally associated with multiple human cancers including cervical cancer (CxCa) and oral squamous cell carcinomas (OSCC) (Forman et al., 2012). HPV-associated cancer is a major global health burden causing nearly half a million deaths worldwide every year. Recent studies have shown that HPV-positive OSCC incidence is increasing at an epidemic rate (Chaturvedi et al., 2011; Stein et al., 2014), suggesting that HPV-positive OSCC will likely comprise the majority of all head and neck cancers (HNC) by 2020 (Auluck et al., 2010; Chaturvedi et al., 2011). This rapid rise in HPV-positive OSCC cases increases the need to improve standard-of-care therapies for this particular subtype of HNC.

While expression of the HPV oncoproteins E6 and E7 quickly inactivates several tumor suppressors, the development of invasive cancer requires many years of viral persistence and disease progression in immunocompetent individuals. Our recent global gene expression analysis of human cervical tissues in different disease stages (normal, early and late precancerous lesions, and cancer) revealed dynamic gene expression changes in a series of cellular pathways, including the cell cycle, translation, mitochondrial energy metabolism, and estrogen signaling (den Boon et al., 2015). Aside from cell cycle- and proliferation-related genes, which are significantly upregulated immediately with high-risk HPV E6 and E7 expression, most host gene expression changes influenced by HPV persistence are slow progressing and accumulating throughout cancer progression. Many of the genes altered slowly and continuously are involved in immune responses and inflammation, such as cytokines and chemokines (den Boon et al., 2015). We have further revealed that restoration of the chemokine CXCL14 in mouse OSCC cells, which is downregulated by HPV E7, significantly suppresses HPV-positive OSCC growth *in vivo* by enhancing NK and T cell infiltration into tumor-draining lymph nodes (Cicchini et al., 2016). These results suggest that HPV-mediated immune dysregulation during virus persistence is important to prevent the elimination of HPV-infected cells during cancer progression. Thus, furthering our understanding of virus-directed immune dysregulation would be critical to develop preventive and therapeutic tools for treating virus-associated cancer as well as eliminating virus-infected cells.

2. Host defense mechanisms against HPV

While the majority of the human population acquires HPV infections, only about 10% to 15% of infected individuals establish life-long persistent infection, and only a subset of which has the potential to progress to invasive cancer (Schiffman et al., 2007). This suggests that, for a majority of HPV-infected individuals, host defense mechanisms are largely effective at eliminating initial HPV infection.

2.1. Physical barriers

The unique lifecycle and strict tropism of HPV generates significant physical barriers for virus entry into basal keratinocytes, the native host cells of HPV. To initiate infection, HPV first needs to translocate across skin and mucous membranes, a process that is facilitated by tissue damage. The mucous membrane poses a major physical barrier to virus infection due to the secretion of a viscous protective fluid and antimicrobial peptides found therein. Once HPV reaches the extracellular matrix, extracellular proteases trigger conformational changes in the virus capsid that facilitates virus internalization. Following uptake of virus particles by macropinocytosis, viruses travel along the endocytic pathway to acidic late endosomes/lysosomes, and retrograde traffics through the Golgi to reach the nucleus (DiGiuseppe et al., 2016; Lipovsky et al., 2013; Pyeon et al., 2009; Schelhaas et al., 2012). During intracellular trafficking, a vast majority of virus particles are degraded and eliminated by host autophagy (Griffin et al., 2013). The nuclear envelope poses another physical barrier to HPV DNA entry into the nucleus. Nuclear envelope breakdown during prometaphase is required for the successful establishment of HPV infection (Pyeon et al., 2009; Schelhaas et al., 2012). Beyond these physical barriers, human α-defensins, particularly α-defensin 5, were found as potent antagonists of HPV infection through inhibition of furin cleavage of the HPV minor capsid protein L2 at the cell surface (Buck et al., 2006; Wiens and Smith, 2015).

2.2. Innate immunity

Once HPV enters a host cell, HPV DNA can be recognized by innate pathogen sensors. Absent in melanoma 2 (AIM2), interferon-γ (IFN-γ) inducible protein 16 (IFI16), and cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS) are cytosolic DNA sensors, while IFI16 also detects foreign DNA in the nucleus (Hornung et al., 2009; Kerur et al., 2011; Li et al., 2013; Unterholzner et al., 2010). Triggering of the AIM2 inflammasome by viral DNA leads to the maturation of caspase-1 and interleukin-1β (IL-1β), which are commonly found activated in HPV16-infected lesions and keratinocytes (Reinholz et al., 2013). IFI16 restricts HPV genome replication and gene transcription by enhancing heterochromatin association with the early and late promoters (Lo Cigno et al., 2015). Further, there is a significant correlation in women between clearance of initial HPV infection and higher expression of nucleic acid-sensing toll-like receptors (TLR3, TLR7, TLR8, and TLR9) as well as TLR2 (Daud et al., 2011). One of the downstream effects of pathogen recognition by pattern recognition receptors (PRRs) is the production of type I interferons (IFN-α and −β). IFN-β treatment hinders HPV entry and promotes clearance of latent HPV episomes in persistently infected cells (Chang et al., 2002; Herdman et al., 2006; Warren et al., 2014). HPV genomes in HPV-positive cervical lesions and IFN-β treated cervical keratinocytes are edited by several IFN-inducible cytidine deaminase APOBEC3 family members (Vartanian et al., 2008; Wang et al., 2014). We and other groups have demonstrated that one of these family members, APOBEC3A, significantly restricts HPV infection (Ahasan et al., 2015; Warren et al., 2015b).