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Review

Host cell restriction factors that limit transcription and replication of human papillomavirus

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ABSTRACT

The life cycle of human papillomaviruses (HPV) is tightly regulated by the differentiation state of mucosal and cutaneous keratinocytes. To counteract viral infection, constitutively expressed cellular factors, which are defined herein as restriction factors, directly mitigate viral gene expression and replication. In turn, some HPV gene products target these restriction factors and abrogate their anti-viral effects to establish efficient gene expression and replication programs. Ironically, in certain circumstances, this delicate counterbalance between viral gene products and restriction factors facilitates persistent infection by HPVs. This review serves to recapitulate the current knowledge of nuclear restriction factors that directly affect the HPV infectious cycle.

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Contents

1. Introduction

The human immune system consists of both adaptive and non-adaptive responses that function to restrict and clear viral pathogens. Adaptive immune responses are tailored specifically to individual pathogens, while non-adaptive immunity (comprised of "intrinsic" and "innate" responses) provides an initial barrier

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to invading pathogens (Iwasaki and Medzhitov, 2015). All three types of immunity (intrinsic, innate, and adaptive) contribute to the restriction and clearance of viral pathogens in humans. The innate immune response is not specific for individual pathogens but is rapidly induced when an invading pathogen is detected. Restriction factors that mediate intrinsic immune responses to pathogens are pre-existing in cells (though they may also be induced) and function to quickly shut down viral infections (Yan and Chen, 2012).

Intrinsic anti-viral immunity is mediated through cellular restriction factors that directly, and immediately, inhibit infection at various steps in the viral life cycle. Viral infection can be restricted upon cell entry, trafficking through the endosome and trans-golgi network, uncoating, or nuclear entry. Restriction factors can also inhibit transcription and translation of viral genes, replication of the viral genome, and assembly/release of viral particles. As described below, the HPV infectious cycle has three main phases: viral entry and establishment; persistent infection in undifferentiated cells; and, productive infection in differentiated cells. Host factors could restrict any of these stages of infection to prevent, or reduce, production of progeny virions. However, one characteristic of intrinsic restriction factors, is that viruses have almost always evolved strategies to evade or counteract the anti-viral function (Yan and Chen, 2012).

Other chapters in this Special Issue will focus on related topics of innate immunity to HPV (Westrich et al., 2017), entry and trafficking of papillomaviruses (DiGiuseppe et al., 2017), and interferon and NFkB induced pathways (Hong and Laimins, 2017). In this article, we will focus on intrinsic nuclear factors that directly restrict papillomavirus replication and transcription.

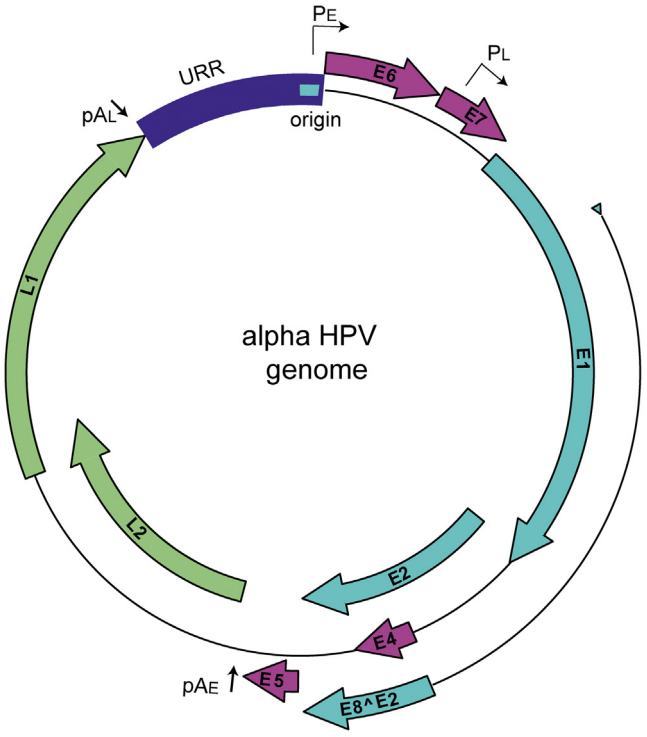

Fig. 1. HPV genome.
Alpha-HPVs have a circular dsDNA genome of approximately 8000 base pairs. Viral ORFs are shown as colored block arrows. Viral early and late promoters are shown as, P_E and P_L, respectively, and polyadenylation sites as pA_E and pA_L. The origin of replication is shown as turquoise bar in the Upstream Regulatory Region (URR).

2. HPV infectious cycle

Papillomaviridae are a family of non-enveloped, DNA viruses that infect a wide spectrum of vertebrate hosts and are trophic for human mucosal and cutaneous keratinocytes. HPVs are associated with a multitude of human pathologies, including benign and malignant tumors (Cubie, 2013). Additionally, a subset of viruses within the alpha genus are deemed "high-risk" HPVs; they are the etiological agents of nearly all cases of human cervical cancer and are highly associated with other cancers such as oropharyngeal carcinoma (Gillison et al., 2000). HPVs have a small, dsDNA genome that is approximately 8000 base pairs in length. All papillomavirus genomes have four core viral open reading frames (ORFs): E1, the viral helicase important for viral genome replication (Bergvall et al., 2013); E2, the helicase loader and major transcriptional regulatory protein (McBride, 2013); E8Ê2, a transcriptional repressor (Dreer et al., 2017); and the major and minor capsid proteins, L1 and L2 (Buck et al., 2013; Wang and Roden, 2013). Moreover, many PVs encode additional ORFs: E4, E5, E6, E7 and E10 (DiMaio and Petti, 2013; Doorbar, 2013; Roman and Munger, 2013; Van Doorslaer and McBride, 2016; Van Doorslaer et al., 2013; Vande Pol and Klingelhutz, 2013). These accessory genes encode products that are involved with cell cycle deregulation, immune evasion and recruitment of host factors for replication. Fig. 1 demonstrates a prototypical HPV genome from the alpha-PV genus, which encodes many of these gene products.

The HPV life cycle is entirely coincident with, and codependent on, the differentiation process of the host epithelium. The virus infects, and establishes a persistent infection in, the basal cells of the epithelium that it accesses through microabrasions. As the infected cells progress through differentiation, viral DNA is amplified, late genes are expressed, and the virus assembles in the most superficial layers of the epithelium (See Fig. 2).

The HPV capsid consists of the two viral proteins, L1 and L2, which are both necessary for infection (Holmgren et al., 2005; Richards et al., 2006). L1 is the major structural capsid protein, and initially interacts with heparan sulfate proteoglycans (HSPGs) on the cell surface (Giroglou et al., 2001; Joyce et al., 1999) and extracellular matrix of the basement membrane of the epithelium (Kines et al., 2009; Selinka et al., 2007). This interaction induces a conformational shift within the capsid that exposes an epitope on the minor capsid protein, L2 (Richards et al., 2006). The virus binds a secondary (as yet uncharacterized) receptor, enters the cell by endocytosis and is trafficked through the endosomal pathways into the trans-golgi network. Many viruses protect their genomes in capsids until viral DNA is delivered to the nucleus. However, HPV is uncoated as it traffics through the endosomal compartment, and L2 is the only capsid protein that remains associated with the viral DNA as it moves to the Golgi network (Day et al., 2013). Finally, the virus arrives at the nuclear membrane, where it requires cell division to occur (resulting in nuclear membrane breakdown) before it gains access to the nucleus (Aydin et al., 2014; Pyeon et al., 2009). Recent evidence shows that the L2-genome complex is delivered to the nucleus in a membranous vesicle that traffics along microtubules and binds host chromosomes, remaining there until the end of mitosis (DiGiuseppe et al., 2016). The viral genome is protected within these vesicles until about four hours after the completion of mitosis.

Early in infection (presumably after the completion of mitosis), the L2:DNA complex becomes localized adjacent to nuclear structures known as Nuclear Domain 10 (ND10) bodies (Day et al., 2004). The L2 protein reorganizes proteins within the ND10 structure, making it conducive as a site for the establishment of transcription and replication of the viral DNA (Becker et al., 2003; Florin et al., 2002). Early viral transcripts are synthesized shortly after infection (Ozbun, 2002), and this is initiated by cellular factors since the HPV virion does not contain any transcriptional regulatory proteins. These early transcripts encode the E1 and E2 viral replication pro-

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