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Mechanisms of persistence by small DNA tumor viruses

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Summary

Virus infection contributes to nearly 15% of human cancers worldwide. Many of the oncogenic viruses tend to cause cancer in immunosuppressed individuals, but maintain asymptomatic, persistent infection for decades in the general population. In this review, we discuss the tactics employed by two small DNA tumor viruses, Human papillomavirus (HPV) and Merkel cell polyomavirus (MCPyV), to establish persistent infection. We will also highlight recent key findings as well as outstanding questions regarding the mechanisms by which HPV and MCPyV evade host immune control to promote their survival. Since persistent infection enables virus-induced tumorigenesis, identifying the mechanisms by which small DNA tumor viruses achieve latent infection may inform new approaches for preventing and treating their respective human cancers.

Introduction

Viral latency is a phase of persistent viral infection in which the virus lies dormant within the host indefinitely and ceases producing large amounts of infectious particles until reactivated. HPV and MCPyV are small DNA viruses that maintain mostly asymptomatic latent infection in the general population, but cause human cancer after many decades [1,2]. Mounting evidence suggests that persistent infection by these two DNA tumor viruses is required for the initiation and development of their associated human cancers [3–7]. For instance, in HPV infected cells, expression of key viral oncogenes inhibits tumor suppressors to cause hyper-proliferation and disordered differentiation of the infected cells [8]. HPV oncogenes also allow the infected cells to escape apoptosis and continue proliferating. Continued expression of the viral oncogenes throughout persistent infection induces host genomic instability, which may result in accumulation of cytogenetic alterations and acquisition of metastatic potential. Over several decades, high-risk HPV infection eventually causes enough genetic and epigenetic changes that drive benign lesions to become metastatic and invasive tumors [8]. MCPyV also infects hosts persistently for decades prior to integration into the host genome and promoting tumorigenesis [7].

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Documented integration events have led to tumor-specific viral oncogene expression patterns, which are the key cancer-activating factors that drive the development of MCPyV-associated Merkel cell carcinoma (MCC) [7,9]. Unlike, HPV-driven cancers, however, MCC lacks a precancerous lesion stage and progresses rapidly at the onset of detectable symptoms.

Because it takes decades for these oncogenic viruses to achieve host cellular transformation, the ability of these viruses to establish persistent infection is critical to incidental viral tumorigenesis. Therefore, mechanisms used by small DNA tumor viruses to achieve persistent latent infection have been a subject of intense investigation for many years. We discuss the recent advances in our understanding of the molecular tactics exploited by these two DNA viruses to establish persistence.

HPV

HPVs comprise a group of small, non-enveloped, double-stranded DNA viruses with a genome of approximately 8,000 base pairs (bp). There are more than 200 genotypes of HPV known to date. Most of HPVs induce benign lesions [10–12]. However, persistent infection with HPVs types classified as high-risk can lead to cervical, anogenital, and oropharyngeal cancers [11,13–15]: contributing to nearly 5% of the worldwide cancer burden [16].

The HPV genome contains coding sequences for six early genes (E1, E2, E4, E5, E6, and E7), which are responsible for viral transcription, replication, and episome maintenance, and two late genes (L1 and L2), which encode the viral capsid proteins [17,18]. HPVs have a specific tropism for squamous epithelial cells. They access cells within the dividing basal epithelial cell layer through microabrasions in the surface epithelium to initiate infection (Figure 1). The later phase of the viral life cycle is completed upon differentiation of infected cells [17]. Most high-risk HPV infections are cleared by the immune system within 1–2 years; however, a subset of these infections persist for decades. Older individuals and those with compromised immune systems are more likely to support chronic HPV infections [3,19]. Individuals with persistent HPV infection have a significantly increased risk of acquiring epithelial cell abnormalities and, subsequently, developing HPV-associated cancers [3,20–22].

Co-opting the host cellular machinery for viral survival

HPV early genes perform functions that establish infection and enable persistence [17]. Among them, E6 and E7 inactivate host tumor-suppressors to promote a cellular environment conducive to viral propagation [8,17]. The early gene, E2, executes dual functions in supporting viral DNA replication and transcription [18,23]. HPV early genes do not perform transcription and replication directly, however. Instead, host DNA replication machinery is recruited to HPV replication centers to produce new progeny [18,24–27]. Furthermore, HPV replication itself induces a state of host genomic instability that activates DNA damage responses (DDRs) [28]. Host DDR factors are also recruited to HPV replication sites to facilitate viral genome amplification [18,29–38], although the mechanistic roles of the DDR factors remain to be elucidated. To benefit fully from the host cellular environment, HPVs also tether their genomes to transcriptionally active domains of

the host genome [39]. This strategy allows HPVs access to chromatin that is free from repressive epigenetic marks and enriched in necessary transcriptional machinery.

Long-term episomal maintenance

During the latent infection period, HPV genomes are maintained as autonomous replicating extrachromosomal elements (episomes) at a low copy number in the nuclei of infected cells [40–43]. To avoid loss of the viral genome in the cytoplasm through degradation or dilution during breakdown and reassembly of the nuclear membrane occurring in each cell cycle, HPV tethers episomes to mitotic chromosomes [44,45]. HPV E2 protein plays a key role in this process by binding to specific sites within the viral genome and nucleating a proteinaceous bridge to condensed mitotic chromosomes [45–52]. A number of cellular proteins, including bromodomain-containing protein 4 (BRD4), DNA topoisomerase 2-binding protein 1 (TopBP1), or CHL1-related helicase gene-1 (ChIR1), have been identified as receptors for the E2/viral genome complex that complete the linkage to host mitotic chromosomes [46,53–56]. Besides hitch-hiking on mitotic chromosomes, E2 proteins encoded by HPV 11, 16, and 18 interact directly with mitotic spindles to maintain HPV DNA as “mini-chromosomes” in dividing cells [57]. HPV E2 viral genome complex tethering to mitotic chromosomes and/or spindles ensures that replicated viral episomes are enclosed within newly assembled nuclear envelopes and partitioned equally among daughter cells after cell division.

Escaping immune surveillance

In order for HPVs to achieve persistent infection, they need to evade host immune detection and eradication. After entry into basal epithelial cells (Figure 1), HPVs deliver their DNA, in complex with the capsid protein L2, to the nucleus by trafficking through the cytoplasm in transport vesicles [58]. During mitosis, HPV-harboring vesicles move along spindle microtubules and transfer HPV genomes to condensed chromosomes [59]. While concealed in the transport vesicles, HPVs avoid exposure to cytoplasmic sensors of foreign DNA, which could trigger an antiviral response [60]. After reaching the nucleus, HPVs replicate at low levels to further reduce the risk of immune detection. During this stage, known as the maintenance replication stage, HPVs establish a reservoir of infection that can persist for decades [3,18,61]. As HPV-infected cells differentiate, the virus enters the vegetative amplification stage in which viral genomes are replicated to high copy numbers. Amplified viral genomes are packaged into capsids once cells are fully differentiated and destined to slough from the surface of the epithelium (Figure 1) [18]. Since immune cells have limited access to the cells near the epithelial surface, elevated HPV genome replication and assembly completed in this last stage of the viral infection cycle tend not to be immunogenic [62].

Before HPV has the opportunity to reach the terminally differentiated upper epithelial layers from which it can infect new hosts, the virus has to persist in the host epithelium for an extended period of time. To avoid immune eradication during this phase, the virus has developed an array of tactics to undermine both innate and adaptive immune responses [63]. For instance, high-risk HPV genome (HPV16, HPV18, or HPV31) present in keratinocytes downregulates transcription of interferons (IFNs), cytokines, and IFN-stimulated genes

(ISGs) [64–67], whereas HPV16 early proteins can act to broadly repress the interferon response [67,68]. In addition, HPV16 E6 and E7 expressed in keratinocytes repress the transcription of Toll-like receptor 9, a critical host innate immune sensor that recognizes both viral and bacterial dsDNA [69]. HPV and encoded proteins also target cGAS-STING, RIG-I, and JAK-STAT immune signaling pathways to inhibit the innate immune response [64,70–72]. Furthermore, HPV16 E6 binds IRF3 and inhibits IFN β production [73], while HPV16 E7 can hamper IRF1 transactivation [74,75].

To evade the adaptive immune response, HPV E5 protein down-regulates expression of major histocompatibility complex (MHC) class I and impedes maturation of MHC class II molecules [76–78]. This E5 function has been suggested to reduce the immune recognition of HPV-infected cells [76–78]. HPV-encoded gene products also influence the composition of the immune cell repertoire in infected tissue through various mechanisms. For instance, HPV E7 represses transcription of the chemokine [C-X-C motif] ligand 14 (CXCL14) gene, which is a potent chemotactic factor that modulates immune cell migration [79]. Both *in vitro* and *in vivo* experiments suggest that the HPV-mediated CXCL14 repression greatly inhibits infiltration of natural killer (NK), CD4 T, and CD8 T cells into the HPV-induced tumor microenvironment [79]. Whether E7 also has the same effect in HPV infected tissues remains unknown.

MCPyV

MCPyV is the only known polyomavirus to cause cancer in humans. MCPyV genomes are found integrated in about 80% of MCC: the context in which MCPyV was discovered [80]. During productive infection of human skin, the ~5,400 bp genome of MCPyV is maintained as circular, double-stranded episome [81]. The viral origin of replication and a bidirectional transcription regulatory region divide the viral genome into the early and late regions [81]. The early region encodes large T (LT) antigen, small T (sT) antigen, the 57kT antigen, a protein called alternative LT ORF (ALTO), as well as an autoregulatory miRNA [81–83]. The late region encodes the capsid proteins, VP1 and VP2 [84].

Evidence for persistent latent infection

Epidemiological evidence suggests that MCPyV establishes asymptomatic, persistent infections in most people. As many as 88% of healthy adults are positive for MCPyV-specific antibodies [85–88]. Serological activity against the MCPyV major capsid protein increases as populations age, from about 10% in early childhood to about 80% in adults [89–91]. MCPyV-specific antibody titers positively correlate with viral load as measured by MCPyV DNA encapsidated in viral particles shed from healthy skin [92,93]. Within a given healthy individual, MCPyV antibody titers remain relatively stable over a period of at least 15 months [92]. By comparison, neutralizing antibody titers to MCPyV, but not other human polyomaviruses, are significantly higher in patients with MCPyV-positive MCC despite the fact that MCC tumors do not express capsid protein [86]. Together, these findings suggest MCPyV has the capacity to persist, and that MCPyV expansion within a host correlates with disease propensity. Inadequate restriction of MCPyV may be a critical factor in enabling MCC development. This hypothesis is supported by the fact that chronic UV-exposure,

advanced age, and HIV-related or iatrogenic immunosuppression pose significant risk for MCC [94–96].

Potential mechanisms of viral latency

Productive MCPyV infections escape elimination by continuous evasion of host immune responses. Incidental integration of the MCPyV genome prohibits further viral replication and can result in cellular transformation. Virus elimination by immune mechanisms and abortive integration are probably prevented by establishing either a constant, low-level replication or fluctuation between a pseudo-latent state and reactivation. Multiple MCPyV-encoded factors have been reported to limit overall MCPyV propagation *in vitro*. For example, expression of the MCPyV LT helicase domain required for the viral DNA replication activates DDR, which limits cellular proliferation [97,98]. Another MCPyV LT domain binds lysosomal cluster protein, hVamp6, which reduces MCPyV replication in 293 cells [99]. In addition, a miRNA encoded by MCPyV can downregulate its early gene transcription [83]. Functions by these MCPyV-encoded factors suggest that the virus has evolved traits to exert suppressive control over its own propagation in order to sustain persistent infection.

With relatively few virally-encoded gene products and narrow tropism, MCPyV coordinates a network of host factors to achieve the optimal level of replication in response to dynamic stimuli [100,101]. As discussed below, at least part of the host control on MCPyV activity comes from immune responses. Rate of MCPyV proliferation is also likely affected by the host cell stemness, nutrient availability, and growth factors present. *In vitro* infection of human dermal fibroblasts parallels the classical wounding response in the skin [102]. Adding serum, epidermal growth factor, fibroblast growth factor, and/or Wnt-signaling activators to MCPyV-infected human dermal fibroblasts each stimulate viral gene expression and replication [102]. A persistence strategy where MCPyV activity level is entrained to fibroblast proliferation would resemble that of HPV in basal epithelial cells.

In contrast, Kwun and colleagues recently proposed an MCPyV latency mechanism by which nutrient starvation reactivates viral replication and transmission in 293 cells [103]. While MCPyV LT is normally targeted for proteasomal degradation by E3 ubiquitin ligases, it is stabilized by nutrient starvation through cooperative interaction of mTOR and MCPyV sT, which prevent LT ubiquitination by the E3 ligases. The involvement of the mTOR pathway in viral latency is an attractive explanation as it has a well-established role in coordinating cell fate and metabolism [104,105]. It is also logical that small DNA viruses with limited coding potential, like MCPyV, would maximize the use of cellular pathways to establish persistence.

Other human polyomaviruses, such as BKV and JCV, have been observed to be “reactivated” from latency in immunocompromised persons who shed higher viral loads and are more susceptible to the respective viral pathologies [106]. Definitive evidence of MCPyV latency, however, has yet to be observed, in part because persistence is a challenging metric to measure *in vitro*. Experiments that span many cell divisions and techniques capable of detecting low copy number viral genomes will be needed to make

progress in this direction. Whether cell culture conditions used with MCPyV are sufficient to mimic the potential latency condition *in vivo* remains an open question as well.

Natural reservoir cells for latent infection

The natural host reservoir cells that maintain latent MCPyV infection have yet to be identified. Primary dermal fibroblasts are the only cell type identified thus far that supports productive MCPyV infection *in vitro* and *ex vivo* (Figure 2) [102]. Growth factors, such as EGF and FGF, which activate and differentiate proliferative fibroblasts at the wound site of human skin, could simulate MCPyV infection (Figure 2) [102]. This observation suggests that MCPyV may gain access to dermal fibroblasts through a cut on the skin (Figure 2). In *ex vivo* skin culture, MCPyV preferentially infects dermal fibroblasts underlying the basal layer of the epidermis and those surrounding hair follicles [102]. Shed MCPyV virions are readily detected in eyebrow hair bulbs [107]. It is tempting to speculate that MCPyV may infect the cells that make up the hair follicle and subsequently use this as a route to disseminate the newly assembled viral progeny particles onto the surface of human skin (Figure 2).

MCPyV may also infect cells at body sites other than the skin to establish a reservoir [108]. For instance, MCPyV DNA was detected in buffy coats of healthy blood donors and inflammatory monocytes of MCC patients, indicating that the virus may establish latent infection in peripheral blood leukocytes [109,110]. In two MCPyV-positive patients with prior history of MCC and active non-melanoma/non-MCC skin cancers respectively, the viral DNA was detected in inflammatory, but not resident monocytes. Presence of MCPyV in inflammatory monocytes in patients with distinct medical histories suggests that the virus may persist and spread in these cells throughout the body [109].

There is no animal model for MCPyV infection; a goal which has proven to be challenging due to the narrow host range of the virus [111]. Lack of an animal model for MCPyV infection presents a major obstacle for identifying potential reservoirs and elucidating the MCPyV infectious cycle. Generation of MCPyV chimeras with mammalian polyomaviruses may provide a solution to its narrow host range in the future [111].

MCC tumors have neuroendocrine characteristics shared with Merkel cells, yet the originating cell of MCC oncogenesis remains a point of debate [112]. Because MCC cells consistently express a number of B-lymphoid lineage markers, pre/pro B-cells have been suggested to be the cellular origin of MCC [112,113]. MCPyV genome is usually found to be integrated into the MCC cellular DNA. This suggests that the origin cells may represent a “dead-end” replication environment that does not support MCPyV propagation and, as such, increases the likelihood of viral genome integration and cellular transformation.

Immune evasion

MCPyV infection can be persistent and is highly prevalent in the general population [87,93,114], suggesting that the virus has evolved mechanisms to escape host immune eradication. Although recent studies have begun to elucidate the MCPyV infectious entry pathways [84,115,116], whether MCPyV traffics through intracellular space using the similar transport vesicles as HPV to evade immune detection has yet to be investigated. On

the other hand, it has been shown that MCPyV gene products may protect the virus or nascently transformed cells from immune destruction. For example, separate groups have reported that MCPyV tumor antigens may downregulate TLR9 or inhibit NF- κ B signaling, and that the MCPyV-encoded miRNA can prohibit NK cell chemotaxis [117–119]. In another study, a microarray analysis revealed that expression of MCPyV LT and sT in hTERT-immortalized BJ human foreskin fibroblasts (BJ-hTERT) leads to upregulation of multiple IFN-induced genes, cytokines and chemokines [120]. Whether these immune response genes are similarly regulated in MCPyV-infected or -transformed cells remains undetermined.

Despite the recent progress made in examining how MCPyV interfaces with the host immune system, nearly all of the studies were performed using transfection or transduction of MCPyV genes into established cancer cell lines. In order to understand how these mechanisms may contribute to MCPyV persistence, it will be important to study them in the context of MCPyV natural infection, and eventually in animal models with dynamic innate and adaptive immune responses. Broad or selective immune suppression could allow uncontrolled proliferation of MCPyV and increase the chance of integration or entry into the original cell of MCC. Factors that maintain the balance between immune restriction and virus evasion will likely play an important role in developing future preventative or therapeutic strategies for MCC.

Conclusions and future perspective

Despite belonging to two different viral families, HPV and MCPyV share many similarities in their biology. Both viruses are commonly shed from apparently healthy human skin surfaces. HPV cannot be propagated in conventional monolayer cell cultures and are strictly tropic for keratinocytes of the skin. The amplification phase of the HPV infectious cycle is triggered by signals that are specific to differentiating keratinocytes. MCPyV, like HPV, replicates poorly in many different types of cells tested in monolayer culture [121]. Productive infection of MCPyV in human dermal fibroblast is stimulated by growth factors and signaling pathways that are induced during wounding and aging process [102]. We therefore suggest that the MCPyV replicative cycle might also be regulated by signaling events present in unique environments of the human skin. In this review, we highlight another parallel between the biology of MCPyV and HPV: while both viruses have genomes with limited coding capacity, they are able to establish persistent and asymptomatic infection for decades prior to inducing human cancer. Despite these biological resemblances, each of the DNA tumor viruses have evolved divergent strategies to exploit and subvert the host cellular machinery to maintain persistent infection. Knowledge gained from studying HPV persistent infection has led to the development of numerous preventive and therapeutic approaches for HPV associated cancers [122,123]. We emphasize that much remains to be learned regarding the MCPyV infectious cycle and chronic infections. It is not known whether MCPyV employs distinct transcriptional programs or whether it tethers episomal DNA to host chromatin like HPV. In addition, how MCPyV manages to effectively escape immune eradication while maintaining persistent infection in the host remains to be elucidated. Because persistent MCPyV infection is crucial for the development of the virus-

driven tumorigenesis, studying these outstanding questions will likely reveal information that is useful for developing therapeutic approaches to prevent MCPyV-induced MCC.

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Highlights

- Both HPV and MCPyV cause human cancer after many decades of latency
- Inadequate restriction of viral infection is critical in enabling cancer development
- HPV and MCPyV co-opt the host cellular machinery for viral propagation
- The viruses evade host immune eradication to promote their survival
- Understanding viral persistence will inform strategies to treat associated cancers

Figure 1.

The HPV infectious cycle. HPV virions (green circles) access basal epithelial cells through microabrasions in the epidermis. HPV genomes replicate at a low level in these cells and are maintained as episomes tethered to host chromatin. Late gene expression and virion production are completed upon keratinocyte differentiation and migration to the outer layers of the epidermis where immune surveillance is reduced. (Not drawn to scale).

Figure 2.

The proposed MCPyV infectious cycle. MCPyV infects human dermal fibroblasts, and not other skin cell types, in *ex vivo* culture. MCPyV infectious particles (yellow circles) may reach the dermal layer through deep abrasions. Fibroblasts closest to the basement membrane and hair follicles support the greatest MCPyV infection in *ex vivo* culture. Cells within the hair follicle may support MCPyV infection or may be a critical route of transmission. (Not drawn to scale).