

## REVIEW ARTICLE

## Viral latency as a driver of epigenetic clock dysregulation and immune aging in cancer development

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## Abstract

Viral latency represents a complex and dynamic balance between persistent viral genomes and the host's immune system, profoundly influencing cellular aging and increasing the risk of cancer through epigenetic reprogramming. This review examines the interconnected mechanisms linking viral latency, epigenetic alterations, and immune system aging, emphasizing their combined contribution to malignancy development. Persistent viral infections, such as those caused by Epstein-Barr virus, human cytomegalovirus, human papillomavirus, and human immunodeficiency virus, disrupt the host's epigenetic machinery, leading to abnormal DNA methylation, histone modification, and chromatin remodeling. These changes accelerate biological aging and silence tumor suppressor genes, creating a cellular environment that favors uncontrolled proliferation. At the same time, chronic immune activation and T-cell exhaustion generate a state of persistent inflammation and immunosuppression that promotes cancer initiation and progression. The review integrates findings from molecular, cellular, and epidemiological studies to highlight key signaling pathways, including nuclear factor kappa B, signal transducer and activator of transcription 3, mechanistic target of rapamycin, and sirtuin pathways, which mediate the interaction between viral persistence and host epigenetic aging. Therapeutic implications are discussed, focusing on the potential use of immune checkpoint inhibitors and biomarker-based precision strategies to counteract virus-associated carcinogenesis. Key research gaps have also been identified, including the need for longitudinal, multi-omic studies to distinguish viral-specific effects from host aging and lifestyle factors. This review provides an integrative framework for understanding how viral latency accelerates biological aging and increases cancer risk, highlighting opportunities for early detection, prevention, and targeted therapeutic interventions.

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## 1. Introduction

Viruses use two distinct replication strategies to reproduce: the lytic and latent (or lysogenic) cycles. The lytic cycle is the active, productive phase of viral infection. During this phase, the virus hijacks the host cell's machinery to express viral genes, replicate

its genome, assemble new virus particles (virions), and ultimately release these virions—often destroying (lysing) the host cell in the process.<sup>1</sup> Conversely, the latent cycle is a dormant or inactive phase in which the viral genome persists within the host cell without producing new infectious virions, keeping the host cell alive.<sup>1</sup> Emerging evidence suggests that such long-term viral latency can profoundly influence host cellular aging mechanisms, particularly through epigenetic alterations that modify DNA methylation patterns. Epigenetic clocks are mathematical models that estimate an individual's biological age by analyzing DNA methylation patterns at specific cytosine-phosphate-guanine (CpG) sites across the genome. Unlike chronological age, which simply counts years, biological age reflects the cumulative effect of genetics, lifestyle, and environmental exposures on the aging process.<sup>2–4</sup> The difference between the predicted biological age and actual chronological age (termed “age acceleration”) can indicate faster or slower aging, and is associated with disease risk and mortality.<sup>5</sup> Importantly, epigenetic age acceleration (EAA) measured by these clocks has been linked to multiple cancers. For instance, colorectal cancer risk and recurrence increase by 20–44% with each decile rise in age acceleration, particularly when measured using GrimAge.<sup>6,7</sup> Lung cancer shows strong associations with PhenoAge and GrimAge acceleration, while bladder cancer risk correlates more with Horvath and Hannum clocks.<sup>8,9</sup>

Aging also profoundly influences immune function through interconnected processes known as immunosenescence, inflammaging, and T-cell exhaustion. Immunosenescence refers to the age-related decline in immune system function, affecting both innate and adaptive immunity. In parallel, inflammaging is a chronic, low-grade inflammatory state that emerges due to the persistent release of pro-inflammatory cytokines and the senescence-associated secretory phenotype (SASP) of aging cells.<sup>10,11</sup> This sustained inflammation promotes tissue dysfunction and contributes to major age-related diseases such as cancer, cardiovascular disease, and neurodegeneration.<sup>10</sup> Chronic antigenic stimulation further drives T-cell exhaustion that exhibits reduced cytokine production, proliferation, and cytotoxic capacity, alongside increased expression of inhibitory receptors such as programmed death protein 1 (PD-1), T-cell immunoglobulin and mucin domain-containing molecule 3, and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).<sup>12,13</sup>

Recent studies consistently show that individuals with

chronic viral infections, such as human immunodeficiency virus (HIV), cytomegalovirus (CMV), and Epstein–Barr virus (EBV), exhibit significant acceleration of biological aging as measured by DNA methylation clocks. HIV infection increases epigenetic age by 5–7 years in blood and brain tissue, with changes detectable even before significant immunosuppression or antiretroviral therapy.<sup>14</sup> Chronic and latent viral infections act as persistent stressors that drive ongoing immune activation and inflammation.<sup>15,16</sup> CMV, in particular, is implicated in reshaping the T-cell pool, promoting clonal expansion and exhaustion, and contributing to the decline in immune diversity and function with age.<sup>16</sup>

Taken together, these findings highlight an urgent need for integrative research that combines epigenetic and immunological pathways to better understand how viral latency contributes to biological aging and cancer development. This review aims to comprehensively examine the complex interplay between viral latency, epigenetic regulation, and immune aging in the context of cancer. It explores the molecular and cellular mechanisms through which latent viral infections disrupt epigenetic clocks, alter gene expression, and accelerate biological aging. Moreover, it examines how chronic immune activation and immune senescence caused by latent infections create a pro-tumorigenic environment that promotes cancer initiation and progression, ultimately aiming to enhance early cancer detection, improve risk stratification, and support the development of novel preventive and therapeutic interventions.

## 2. Methodology

A structured literature search was conducted for this review using five electronic databases, including MEDLINE (EBSCO), Cochrane Central Register of Controlled Trials, PubMed, PubMed Central, and Google Scholar. Studies exploring the relationship between viral latency, epigenetic dysregulation, immune aging, and cancer were considered. Search terms included “viral latency,” “epigenetic clock,” “DNA methylation,” “epigenetic age acceleration,” “immunosenescence,” “inflammaging,” “T-cell exhaustion,” “chronic viral infection,” “EBV,” “CMV,” “HIV,” “HPV,” “HBV,” and “cancer,” with Boolean operators used to refine results. The search date was set to November 2025, with a focus on recently published literature to ensure the information is relevant to current practice. Additional studies were identified by searching the reference lists of the retrieved articles. The inclusion criteria consisted of peer-reviewed articles written in English. Studies were included

if they provided mechanistic, clinical, or epidemiological evidence linking chronic or latent viral infections with epigenetic alterations, immune aging, or cancer risk.

### 3. Viral latency and its molecular landscape

Viral latency is characterized by three main features: (i) the persistence of the viral genome within the host cell, (ii) highly restricted or minimal viral gene expression with no production of infectious viral particles, and (iii) the capacity for the virus to reactivate and resume productive (lytic) replication under certain conditions.<sup>2</sup> This state allows the virus to evade immune detection and persist within its hosts for extended periods, often for a lifetime. Latency exists along a spectrum that includes true latency, pseudolatency (persistent infection), and episomal or integrated latency. In true latency, as seen in herpes simplex virus and EBV, the viral genome is maintained as an episome in host cells with most genes epigenetically silenced—only a few latency-associated transcripts or proteins, such as latency-associated transcript (LAT) in herpes simplex virus and Epstein–Barr nuclear antigen 1 or latent membrane proteins (LMPs) in EBV, remain active to preserve dormancy.<sup>17,18</sup> In pseudolatency, viruses such as CMV and HIV persist within host cells while employing immune evasion strategies. CMV, for instance, encodes multiple immune-modulatory proteins, while HIV persists through reservoirs of infected cells and ongoing low-level replication.<sup>19,20</sup> Mechanistically, episomal latency involves circular viral genomes tethered to host chromatin and regulated by viral or host epigenetic factors, whereas integrated latency, as in HIV or human papillomavirus (HPV), entails the insertion of viral DNA into the host genome, allowing long-term persistence but complicating eradication due to potential reactivation and stable genomic integration.<sup>17,20,21</sup>

#### 3.1. Molecular regulation of latency

Host cells employ multiple epigenetic mechanisms to silence viral genes, thereby restricting viral replication and maintaining latency. One key mechanism involves histone modifications. Repressive histone marks such as H3K9me3 and H3K27me3, added by host enzymes, including SET domain bifurcated histone lysine methyltransferase 1 and enhancer of zeste homolog 2, promote heterochromatin formation and transcriptional silencing, which is essential for maintaining viral latency.<sup>22</sup> In parallel, host DNA methyltransferases add methyl groups to CpG islands within viral promoters, resulting in long-term transcriptional repression.<sup>22</sup> This mechanism is particularly well-established in the silencing of latent HIV and EBV promoters, where DNA methylation acts synergistically with histone modifications to maintain

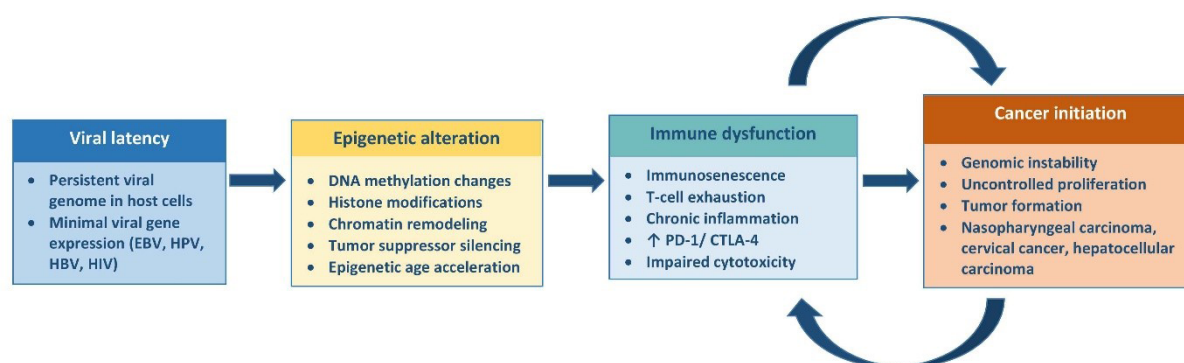
viral quiescence.<sup>23</sup> In addition to these mechanisms, latent viruses can influence host chromatin structure and nuclear organization. Episomal or integrated viral genomes form three-dimensional chromatin interactions with host DNA, modulating both viral and host gene expression through chromatin looping and noncoding RNAs.<sup>23</sup> Some viruses, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and African swine fever virus, induce global changes in host chromatin structure, including compartment mixing, heterochromatinization (enrichment of H3K9me3 and H3K27me3), and altered enhancer–promoter interactions, leading to widespread transcriptional reprogramming and immune evasion.<sup>24</sup>

#### 3.2. Immune evasion mechanisms and clinical significance

Many viruses evade immune detection by downregulating major histocompatibility complex class I molecules on infected cells, impairing cytotoxic CD8<sup>+</sup> T-cell recognition and promoting viral persistence. Viruses such as SARS-CoV-2, influenza, Kaposi's sarcoma-associated herpesvirus (KSHV), and adenoviruses achieve this by disrupting major histocompatibility complex class I expression, trafficking, or transcription.<sup>25</sup> Chronic viral infections also alter cytokine signaling, often elevating immunosuppressive cytokines like interleukin-10, which suppress antiviral responses and sustain infection.<sup>25,26</sup> Persistent antigenic stimulation further drives T-cell exhaustion, characterized by reduced effector function, diminished cytokine production, and upregulation of inhibitory receptors such as PD-1 and CTLA-4.<sup>27,28</sup> These exhausted T cells undergo epigenetic and metabolic reprogramming, weakening immune control over infections and tumors.<sup>27,28</sup> Over time, chronic viral latency fosters inflammation, genomic instability, and a permissive tissue environment that facilitates cancer development, as observed in infections such as HIV, hepatitis B virus (HBV), hepatitis C virus, and EBV (Figure 1).<sup>27</sup>

### 4. Relevance of epigenetic clocks to viral latency

Several DNA methylation clocks have been developed to estimate biological aging with varying levels of precision. The Horvath clock, introduced in 2013,<sup>3</sup> is a pan-tissue model that uses 353 CpG sites across multiple tissues to accurately predict chronological age, while the Hannum clock,<sup>4</sup> introduced in the same year, relies on 71 CpG sites measured in blood and shows a strong correlation with age. Advancing beyond simple age prediction, second-generation clocks such as PhenoAge<sup>5</sup> incorporate CpG sites linked to both chronological age and clinical biomarkers (e.g., blood cell counts, creatinine), enhancing their



**Figure 1.** Schematic flow of viral latency-induced epigenetic alterations and immune dysfunction leading to cancer initiation

Abbreviations: CTLA-4: Cytotoxic T-lymphocyte-associated antigen 4; EBV: Epstein–Barr virus; HBV: Hepatitis B virus; HIV: Human immunodeficiency virus; HPV: Human papillomavirus; PD-1: Programmed death protein 1.

ability to predict health span and mortality risk. The most recent and comprehensive model, GrimAge,<sup>6</sup> integrates methylation-based surrogates for plasma proteins and smoking history, demonstrating superior performance in predicting disease risk, lifespan, and all-cause mortality.

Several viruses encode proteins that actively manipulate the host's epigenetic machinery to promote viral persistence, immune evasion, and oncogenesis. For instance, EBV expresses LMP1, which activates DNA methyltransferase 1 (DNMT1) via the c-Jun N-terminal kinase–activator protein-1 pathway, leading to hypermethylation and silencing of tumor suppressor genes, such as *CDH1*.<sup>29</sup> Another EBV protein, Epstein–Barr nuclear antigen 1, contributes to genomic instability and alters host DNA methylation patterns.<sup>30</sup> Similarly, HPV employs its E6 and E7 oncoproteins to upregulate DNMTs, causing widespread changes in DNA methylation and dysregulation of genes involved in apoptosis and cell cycle control.<sup>31</sup> E7 also modifies histone methylation and acetylation by interacting with histone-modifying enzymes (e.g., suppressor of variegation 3–9 homolog 1, lysine demethylase 6A/B, SET domain-containing protein 7), leading to silencing of immune sensor genes and inhibition of p53 function.<sup>31</sup> These virus-induced epigenetic alterations collectively remodel the host methylome, leading to detectable shifts in DNA methylation age as measured by epigenetic clocks. Key viral proteins, their epigenetic targets, and the effects on biological aging and cancer risk are summarized in Table 1.

Several chronic viral infections are strongly associated with accelerated epigenetic aging and immune dysfunction. CMV seropositivity correlates with increased DNA methylation age across both young and elderly individuals, suggesting that CMV infection advances biological aging

beyond chronological age and contributes to immune dysregulation through altered T-cell populations and increased markers of immunosenescence.<sup>32</sup> Similarly, EBV latency drives age-like DNA methylation changes in B cells, especially in genes governing immune function and cell cycle regulation, mimicking patterns of natural aging.<sup>33</sup> Moreover, emerging evidence suggests that viral microRNAs may play a role in driving epigenetic drift, which refers to gradual, stochastic changes in DNA methylation over time.<sup>33,34</sup> Viral microRNAs can target host epigenetic regulators, further promoting methylome remodeling and potentially accelerating biological aging, though this mechanism requires deeper investigation in human models.<sup>33,34</sup>

## 5. Immune aging and inflammaging in chronic viral latency

Aging profoundly impacts immune system function through interconnected processes known as immunosenescence, inflammaging, and T-cell exhaustion. One of the earliest hallmarks of immunosenescence is thymic involution, characterized by a progressive loss of thymic epithelial tissue, increased adiposity, and reduced thymopoiesis. As a result, naïve T-cell output declines, shrinking the T-cell receptor repertoire and impairing the body's ability to respond to new antigens.<sup>10,35,36</sup> This loss of immune diversity contributes to increased susceptibility to infections, reduced vaccine efficacy, and a higher incidence of cancer in older adults.<sup>10,35,36</sup> Inflammaging is a chronic, low-grade inflammatory state that emerges as a defining feature of aging immunity. This persistent inflammation is characterized by elevated cytokines such as interleukin-6 and tumor necrosis factor alpha and is fueled by senescent immune cells, lifelong antigenic exposure, and persistent viral infections, particularly CMV. The accumulation of

Table 1. Viral proteins, epigenetic targets, and impact on aging and cancer risk

Virus	Viral protein/mechanism	Epigenetic target	Impact on epigenetic clock/aging	Associated cancer
EBV	LMP1	DNMT1, H3K27me3	Induces hypermethylation of tumor suppressor genes; accelerates epigenetic age	Nasopharyngeal carcinoma, Hodgkin lymphoma
	EBNA1	Global DNA methylation, chromatin structure	Alters the host methylome, contributes to genomic instability	Burkitt lymphoma, nasopharyngeal carcinoma
HPV	E6	DNMTs	Silences tumor suppressors; epigenetic age acceleration; promote p53 degradation	Cervical cancer, anal cancer
	E7	DNMTs, histone modifiers (SUV39H1, KDM6A/B, SET7)	Alters DNA methylation and histone marks	Cervical cancer
HBV	HBV X protein	DNMTs, Histone acetylation	Silences tumor suppressor genes; promotes epigenetic aging	Hepatocellular carcinoma
HIV	Tat	SIRT1, NF- $\kappa$ B	Disrupts sirtuin activity; increases inflammatory transcription; contributes to immune aging	Acquired immunodeficiency syndrome-related cancers
CMV	Various immune-modulatory proteins	Chromatin remodeling enzymes	Alters T-cell populations, accelerates immune aging	Increased risk of multiple cancers indirectly via immune dysregulation
KSHV	vIL-6	STAT3, chromatin modifiers	Promotes latency and immune evasion; contributes to cellular aging	Kaposi's sarcoma

Abbreviations: CMV: Cytomegalovirus; DNMT: DNA methyltransferase; EBNA1: Epstein–Barr nuclear antigen 1; EBV: Epstein–Barr virus; HBV: Hepatitis B virus; HIV: Human immunodeficiency virus; HPV: Human papillomavirus; KDM6A/B: Lysine demethylase 6A/6B; KSHV: Kaposi's sarcoma-associated herpesvirus; LMP1: Latent membrane protein 1; NF- $\kappa$ B: Nuclear factor kappa B; SET7: SET domain containing lysine methyltransferase 7; SIRT1: Sirtuin 1; STAT3: Signal transducer and activator of transcription 3; SUV39H1: Suppressor of variegation 3–9 homolog 1; Tat: Trans-activator of transcription; vIL-6: Viral interleukin 6.

autoreactive T cells due to impaired thymic selection further amplifies this inflammatory milieu, creating a feedback loop of immune dysfunction and tissue damage.<sup>10,35,36</sup> At the molecular level, aging immune cells exhibit impaired DNA repair mechanisms, telomere shortening, and increased genomic instability, particularly in clonally expanded T cells. These changes accelerate cellular senescence and deepen the functional decline of immune responses.<sup>10,11</sup> Importantly, chronic viral infections such as HIV, CMV, and herpesviruses mimic and exacerbate these aging-related processes through persistent antigenic stimulation and epigenetic remodeling.

### 5.1. Epigenetic remodeling in immune aging and viral latency

Both aging and chronic viral latency drive overlapping epigenetic changes in immune cells, including alterations in DNA methylation and chromatin structure that stabilize

dysfunctional T-cell states. Studies have shown that immunosenescent cells and latently infected cells share similar methylation signatures. For instance, latent HIV and herpesvirus genomes accumulate CpG methylation over time, mirroring the age-related methylation drift observed in host T cells.<sup>37,38</sup> These methylation marks reinforce transcriptional silencing and are linked to diminished immune responsiveness. Persistent antigen exposure during chronic infection further induces stable epigenetic remodeling in T-cell subsets, such as histone modifications and chromatin accessibility changes that lock T cells into exhausted or senescent states.<sup>28,37</sup> These “epigenetic scars” remain even after antigen clearance, preventing full immune recovery and contributing to long-term immunological aging.

Several key signaling pathways also act as central regulators connecting immune aging with viral latency, including nuclear factor kappa B (NF- $\kappa$ B), signal transducer

and activator of transcription 3 (STAT3), mechanistic target of rapamycin (mTOR), and sirtuins (SIRT).<sup>28,39</sup> NF- $\kappa$ B and STAT3 promote inflammation and T-cell exhaustion, whereas mTOR and SIRT pathways influence metabolism, chromatin state, and cellular longevity.<sup>28,39</sup>

## 5.2. Nuclear factor kappa B signaling in inflammaging and viral persistence

The role of NF- $\kappa$ B is central to the regulation of inflammatory gene expression and T-cell activation. Its chronic activation represents a key attribute of both aging-associated inflammaging and persistent viral infection. In HIV infection, the viral trans-activator of transcription protein, produced early in the HIV infection cycle, increases HIV-1 replication exponentially by activating NF- $\kappa$ B signaling to enhance viral transcription, while simultaneously sustaining a pro-inflammatory environment that promotes T-cell exhaustion.<sup>40</sup> Similarly, EBV LMP1 constitutively activates NF- $\kappa$ B, mimicking CD40 signaling to promote cell survival and chronic inflammation.<sup>41</sup> This, in turn, reinforces latency and immune dysfunction and contributes to the expansion of senescent immune cell populations, as observed in older individuals.

## 5.3. Signal transducer and activator of transcription 3 signaling and T-cell exhaustion

Signal transducer and activator of transcription 3 signaling is another critical pathway that links viral latency to immune aging. Chronic STAT3 activation promotes immunosuppressive cytokine production, impairs effector T-cell responses, and drives skewing toward exhausted phenotypes.<sup>42</sup> Several viruses exploit this pathway to establish and maintain latency. For example, EBV LMP1 and KSHV viral interleukin-6 activate STAT3 signaling.<sup>43</sup> This promotes cell survival and suppresses antiviral immunity. In the context of aging, persistent STAT3 activation overlaps with age-related immune suppression, further compounding the decline in T-cell function and contributing to ineffective viral clearance.

## 5.4. Sirtuin pathways as modulators of longevity and viral latency

Sirtuins, particularly SIRT1 and SIRT6, function as epigenetic and metabolic regulators that promote genomic stability and longevity. These proteins negatively regulate NF- $\kappa$ B and mTOR signaling, thereby restraining inflammation and cellular aging.<sup>44</sup> Viral proteins can disrupt sirtuin activity, favoring latency. HIV trans-activator of transcription protein inhibits SIRT1, resulting in enhanced NF- $\kappa$ B acetylation and sustained inflammatory transcription, while herpesviruses have

been shown to interfere with sirtuin-mediated chromatin silencing to maintain latent viral genomes.<sup>40,45</sup> Age-related declines in sirtuin activity further exacerbate these effects by reducing the host's ability to counterbalance chronic inflammation and epigenetic dysregulation.

## 6. Viral latency, epigenetic aging, and oncogenesis

Viral-driven carcinogenesis is characterized by chronic inflammation, genomic instability, immune escape, and epigenetic dysregulation. Several persistent viruses, such as EBV, HPV, HBV, and HIV, are strongly linked to specific human cancers, often through both direct viral effects and indirect immune-mediated mechanisms.<sup>46</sup>

### 6.1. Viral-driven carcinogenesis

Viral carcinogenesis is driven by a complex interplay of mechanisms that collectively create a cellular environment conducive to uncontrolled proliferation and malignant transformation. Persistent viral infections, such as those caused by HBV and hepatitis C virus, induce chronic inflammation characterized by continuous tissue damage, immune cell infiltration, and cytokine release, creating a pro-tumorigenic microenvironment.<sup>47,48</sup> At the genomic level, integration of viral DNA, particularly from HBV and HPV, can disrupt host genes, leading to mutations, chromosomal rearrangements, and activation of oncogenes or silencing of tumor suppressor genes.<sup>47-49</sup> To ensure persistence, oncogenic viruses evade immune detection by impairing antigen presentation, altering cytokine signaling, and promoting T-cell exhaustion, allowing infected cells to survive and accumulate further mutations.<sup>48</sup> Similarly, viral proteins such as HBV X protein and HPV E6/E7 reprogram host epigenetic machinery through DNA methylation, histone modification, and noncoding RNA regulation, silencing tumor suppressor genes and activating oncogenic pathways.<sup>47,49</sup>

### 6.2. Mechanistic links between epigenetic aging and cancer risk

Epigenetic aging, characterized by age-related changes in DNA methylation patterns, is intricately linked to cancer risk through mechanisms that promote genomic instability, tumor suppressor gene silencing, and virus-induced molecular changes. Accelerated epigenetic aging correlates with increased genomic instability and mutational burden, as global hypomethylation and site-specific hypermethylation disrupt DNA repair genes (e.g., MutL homolog 1) and promote chromosomal aberrations, creating a permissive environment for oncogenesis.<sup>50</sup> Multiple studies provide converging evidence for this relationship. Soto-Palma *et al.*<sup>50</sup> demonstrated that genome

integrity erodes with age, leading to increased DNA lesions and transcriptional disruptions. Additionally, Yan *et al.*<sup>51</sup> found positive associations between epigenetic mutation load and multiple EAA measures (meta-analysis correlation ranging from  $r = 0.109$  to  $0.179$ ). Koch *et al.*<sup>52</sup> specifically showed that CpG mutations coincide with methylation changes, creating a “one-to-many mapping” that allows mutation-based predictions of age. Vijg and Suh<sup>53</sup> further confirmed that random genomic alterations can lead to functional decline, with mutations accumulating across various organs and tissues. Oncogenic viruses such as HPV and EBV induce hypermethylation of tumor suppressor genes, including *CDKN2A* and *RASSF1A*, silencing their expression and impairing cell cycle regulation and apoptosis, which are critical for preventing tumor formation.<sup>54</sup> Moreover, viral latency mimics “molecular aging” by sustaining chronic epigenetic alterations and inflammation, further predisposing cells to oncogenic transformation, as seen in cancers such as cervical and nasopharyngeal carcinoma.<sup>55,56</sup>

### 6.3. Immune aging as a tumor-promoting factor

Immune aging, or immunosenescence, promotes tumor development by weakening antitumor defense mechanisms and creating a pro-inflammatory environment that supports cancer initiation and progression. One of the key features of immune aging is T-cell exhaustion, marked by diminished proliferation, cytokine production, and cytotoxic activity.<sup>57</sup> The upregulation of inhibitory receptors such as PD-1, CTLA-4, and T-cell immunoglobulin and mucin domain-containing molecule 3 further limits the ability of exhausted T cells to recognize and eliminate emerging tumor cells, allowing malignant clones to escape immune control.<sup>57,58</sup> Concurrently, chronic low-grade inflammation associated with aging (i.e., inflammaging) drives continuous production of reactive oxygen species, leading to oxidative DNA damage, genomic instability, and mutations that initiate tumorigenesis.<sup>59,60</sup> Aging tissues also develop a distinct microenvironment enriched with senescent cells that express SASP markers, characterized by the secretion of pro-inflammatory cytokines, growth factors, and matrix-remodeling enzymes.<sup>61,62</sup> While SASP can initially act as a tumor-suppressive mechanism by limiting the proliferation of damaged cells, it can later shift toward promoting angiogenesis, epithelial-to-mesenchymal transition, and tumor proliferation.<sup>61,62</sup> Its ability to remodel the surrounding tissue microenvironment and influence neighboring cells makes SASP a dynamic and context-dependent process with profound implications for age-related cancer development.<sup>62</sup>

## 7. Therapeutic and research implications

Targeting the epigenetic alterations induced by viral latency offers promising avenues for therapy. DNMT inhibitors such as azacitidine and histone deacetylase inhibitors have shown efficacy in reactivating silenced tumor suppressor genes and suppressing viral oncogene expression in virus-associated cancers.<sup>63,64</sup> Additionally, therapeutic strategies aimed at disrupting viral latency maintenance genes, such as those controlling chromatin remodeling and methylation, may help reverse virus-induced EAA and restore normal cellular function.<sup>65</sup> Importantly, viruses are not solely oncogenic; they can be repurposed as tools against cancer. Engineered oncolytic viruses, for instance, are designed to selectively infect and kill cancer cells. This highlights a therapeutic approach that contrasts with the oncogenic effects of persistent latent viral infections.<sup>66</sup>

Immunotherapies designed to rejuvenate the aging or exhausted immune system are gaining traction for the management of virus-associated malignancies. Immune checkpoint inhibitors, such as PD-1 and CTLA-4 blockers, can reinvigorate exhausted T cells by “releasing the brakes” on their suppressed activity, thereby restoring their immune and antitumor functions.<sup>67</sup> Furthermore, vaccines targeting latent viral antigens, such as EBV gp350, hold potential for preventing viral reactivation and reducing cancer risk by enhancing immune recognition of infected cells.<sup>68</sup>

Epigenetic age acceleration holds great promise as a biomarker for identifying individuals at heightened risk of virus-induced cancers. DNA methylation signatures derived from viral latency studies can be used to stratify high-risk populations, track disease progression, and guide early intervention strategies. By enabling personalized risk assessment, these biomarkers could significantly enhance outcomes through precision oncology, as demonstrated by a study on EBV, showing that low DNA methylation patterns distinguish lytic from latent viral states with 93.3% sensitivity and 97.2% specificity.<sup>69</sup>

Public health strategies should prioritize screening for latent viral infections, especially among aging and immunocompromised populations at higher risk of reactivation. Incorporating epigenetic aging metrics into clinical evaluations can improve early detection of virus- and age-related cancers. A comprehensive approach that combines preventive vaccination, lifestyle interventions, and routine monitoring of biological age markers offers a promising pathway to reduce the global burden of viral carcinogenesis.<sup>70</sup>

## 8. Challenges, gaps, and future directions

Despite growing evidence linking viral latency to EAA and immune dysfunction, significant challenges remain



in fully understanding and translating these findings into clinical practice. One of the foremost gaps is the lack of longitudinal, multi-omic studies that can trace how persistent viral infections influence epigenetic clock trajectories over time. Integrating multi-layered omics data, including transcriptomic, proteomic, metabolomic, and epigenomic profiles, alongside immune aging markers, would provide a more comprehensive understanding of how viral latency reprograms cellular networks across molecular levels. Furthermore, there is an urgent need to standardize epigenetic clock models across tissues and populations, as variability in clock performance hinders comparability between studies and reduces their clinical applicability.<sup>71-73</sup> Developing tissue-specific and virus-sensitive clocks could help capture more precise biological signals related to latent infections. Another major challenge lies in disentangling viral-specific effects from confounding factors, such as lifestyle, environmental exposures, and comorbidities, which also influence epigenetic aging and immune function.<sup>74,75</sup> This requires well-characterized cohorts with detailed demographic, clinical, and behavioral data to accurately isolate viral contributions. Looking ahead, future research should prioritize interdisciplinary collaboration among virologists, immunologists, and computational biologists to develop integrative models that link viral persistence to cellular aging and cancer risk. Advances in single-cell and spatial epigenomics, along with artificial intelligence-driven modeling, offer exciting opportunities to map viral–host interactions at unprecedented resolution. Ultimately, bridging these gaps will pave the way for precision interventions that not only target viral reactivation and epigenetic dysregulation but also mitigate age-related cancer susceptibility in at-risk populations.

## 9. Conclusion

In summary, viral latency plays a pivotal role in accelerating biological aging and promoting cancer development through interconnected epigenetic and immune mechanisms. Persistent infections such as EBV, CMV, HBV, and HIV remodel DNA methylation patterns, disrupt chromatin architecture, and induce EAA, while chronic immune activation and inflammation lead to immune exhaustion and a pro-tumorigenic environment. Together, these processes create a self-perpetuating cycle of epigenetic dysregulation and immune dysfunction that increases cancer susceptibility. Advancing research through longitudinal, multi-omic studies and standardized epigenetic clock models will be essential to disentangle viral effects from host aging. Integrating epigenetic and immunologic biomarkers into preventive and therapeutic frameworks could enable earlier cancer detection, targeted

interventions, and precision strategies to mitigate the long-term impact of latent viral infections on aging and malignancy.

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