Review

Discovery Medicine 2026; 38(207): 1007–1026
https://doi.org/10.24976/Discov.Med.202638207.81

The Impact of Viral Immune Evasion on the Development of Childhood Cancer: The Role of Cytomegalovirus

Pamela Ruvalcaba-Hernández[1,2], Juan Carlos Nuñez-Enriquez[3], Minerva Mata-Rocha[4], Elva Jiménez-Hernández[5], Juan Manuel Mejía-Aranguré[6], Silvia Patricia Melchor-Doncel[1], Angélica Rangel-López[1], Juan Xicohtencatl-Cortes[7], SA Ochoa[7], Ariadnna Cruz-Cordova[8], José Arellano-Galindo[1,9,*]

[1]Laboratorio de Virología, Hospital Infantil de México Federico Gómez, 06720 Ciudad de México, Mexico
[2]Posgrado en Ciencias Biológicas, Universidad Nacional Autónoma de México, 04510 Ciudad de México, Mexico
[3]Unidad de Investigación Médica en Epidemiología Clínica, Hospital de Pediatría, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, 06720 Ciudad de México, Mexico
[4]Unidad de Investigación en Genética Humana, Hospital de Pediatría, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, 06720 Ciudad de México, Mexico
[5]Hospital Pediátrico Moctezuma Secretaría de Salud, Universidad Autónoma Metropolitana, 15530 Ciudad de México, Mexico
[6]Laboratorio de Genómica Funcional del Cáncer, Instituto Nacional de Medicina Genómica, 14610 Ciudad de México, Mexico
[7]Laboratorio de Bacteriología Intestinal, Hospital Infantil de México Federico Gómez, 06720 Ciudad de México, Mexico
[8]Laboratorio de Inmunoquímica, Hospital Infantil de México Federico Gómez, 06720 Ciudad de México, Mexico
[9]Departamento de Medicina, Centro Interdisciplinario de Ciencias de la Salud Unidad Milpa Alta, Instituto Politécnico Nacional, 12000 Ciudad de México, Mexico

*Correspondence: josearellanogalindo@yahoo.com.mx; jarellanog@ipn.mx (José Arellano-Galindo)

Submitted: 12 June 2025 Revised: 12 November 2025 Accepted: 26 November 2025 Published: 20 April 2026

During the interaction between a virus and its host, a complex interplay arises between the host's defence mechanisms and the viral survival strategies. This interaction impacts not only viral replication and the viral lifecycle but also affects the host's homeostasis, including cellular genetics and immune responses. The outcomes of host-virus interactions can vary widely, ranging from successful pathogen clearance to severe disease or even death, influenced by factors such as host genetics, age, comorbidities, and environmental conditions. Viruses adeptly manipulate cellular machinery and metabolism, reprogram signalling pathways, and undermine immune responses to enhance their survival. A key strategy employed by viruses is immune evasion, utilising various techniques to bypass the host's immunovigilance. These strategies not only encourage persistent infections but also raise concerns about oncogenic potential, particularly in hematologic malignancies like acute lymphoblastic leukaemia (ALL). Such mechanisms may play a pivotal role in the alterations induced by viral contributions that disrupt immune surveillance and foster malignancy. This review seeks to elucidate the potential role of human cytomegalovirus (HCMV) as a risk factor and etiological contributor to the development of ALL in children. Although HCMV has not been officially recognized as an oncogenic virus, emerging evidence suggests that early-life infection may predispose to malignant transformation by promoting oncogenic pathways and immune dysregulation.

Keywords: virus; human cytomegalovirus; cancer; oncogenesis; acute lymphoblastic leukaemia

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Introduction

The coevolution of viruses and their hosts is underpinned by host defence strategies and viral countermeasures that have evolved over many years. These mechanisms can manipulate cellular processes, reprogram metabolism, and subvert immune detection [1–3]. The balance between viral replication and host clearance, determined by specific host-virus interactions, underlies outcomes ranging from asymptomatic persistence to severe disease or death [4,5]. The host immune system plays a crucial role in determining the outcome of these viral mechanisms, which enable viruses to adapt to specific hosts, enhance replication efficiency, prolong infectivity, and evade immune responses [1,4]. These are also further modulated by host factors such as susceptibility, immune competence, and the nature of commensal or antagonistic interactions [6,7].

Viral strategies not only facilitate replication and dissemination but also contribute to disease pathogenesis by altering signalling pathways and disrupting host homeostasis [2,5]. Additionally, factors such as age, sex, genetics, comorbidities, nutritional status, and environmental exposures further influence host vulnerability and disease progression [1,7,8]. Moreover, viral mutations can enhance infectivity, alter virulence, and drive cross-species transmission, especially under selective pressures that favour increased fitness and pathogenicity [9–11].

To sustain replication, both DNA and RNA viruses rewire host metabolism, particularly affecting carbon flux, glycolysis, and the pentose phosphate pathway, thereby enhancing the biosynthesis of essential macromolecules for virion assembly and functional protein modification [3,12]. These interactions reshape protein networks through mutations, convergent evolution, and epigenetic alterations, which influence immune detection and responses and may induce or worsen disease development [13–17].

One of the most critical aspects of viral pathogenesis is immune evasion. Upon infection, the host initiates innate immune responses, the first line of defence, which involves epithelial and endothelial barriers, as well as the activation of various immune cells, including macrophages, neutrophils, mast cells, and natural killer (NK) cells [18–20]. These responses activate inflammatory signalling cascades that recruit adaptive immune components such as B and T lymphocytes, and allow antigen presentation to eliminate the pathogen [21]. Nevertheless, viruses have evolved mechanisms to inhibit or modulate these responses, primarily through the encoding of specific proteins, thereby increasing the risk of persistent infections, immunopathology, and, in some cases, oncogenesis [22,23].

These viral mechanisms are yet to be fully understood; however, it has been recently described that proteins encoded by viruses can disrupt key signalling pathways related to antigen presentation, immune cell activation, viral RNA and DNA sensing, antiviral responses, host gene transcription, antibody recognition, and cell exhaustion. Viruses like Human Immunodeficiency (HIV), Herpes simplex (HSV), Human cytomegalovirus (hCMV), Epstein-Barr (EBV), influenza and SARS-CoV-2 are known to inhibit *Toll-like receptors* (*TLR*), *pattern-recognition receptors* (*PRRs*), *RIG-I/MDA5*, *cGAS-STING*, *MHC class I*; dysregulate *IFN* production (type I and III), *JAK/STAT* pathway; manipulate autophagy, inflammasome and pyroptosis, caspases, cell compartmentalisation/virosomes and mimic host proteins producing virokines and viroreceptors (Fig. 1) [24–30].

The encoding and expression of proteins during both lytic and latent phases are directly or indirectly involved not only in a successful immune evasion but also in the development of more severe diseases, such as autoimmunity and cancer [22,31]. To date, the correlation between early infections and childhood malignancies is gaining relevance. Certain viruses are responsible for multiple disruptions in the cell cycle signalling, changes in cytokine and chemokine profiles, gene alterations, and weakened immune responses in foetuses and newborns [32].

From Epidemiology to Genomics: Genetic and Viral Factors in Childhood Acute Lymphoblastic Leukaemia

Childhood cancer development has multifactorial origins, many of which remain unknown; however, it is the second leading cause of death in children under 15 years of age, surpassed only by accidental injuries and poisoning [33]. The incidence is estimated to be 103 to 208 cases per million, which translates to 200,000–400,000 new diagnoses [33,34]. The type of cancer varies with age, race/ethnicity and gender, e.g., acute lymphoblastic leukaemia (ALL) (~26%), tumours of the Central Nervous System (~20%), and kidney, liver and neuroblastoma (~7%) are more frequent in children under 10 years old; in addition, males and non-Hispanic whites are more susceptible [35]. Demographic, perinatal, environmental, and genetic factors have been associated with a greater susceptibility, as well as congenital and structural birth defects, which increase the risk because of the high rates of mutation and DNA damage [35,36].

In the United States, ALL constitutes approximately 75% of leukaemia diagnoses in individuals under 20 years of age, making it the most frequently occurring childhood haematological malignancy. It is characterised by the clonal proliferation of immature lymphoid progenitor cells of either B-cell or T-cell lineage, most commonly presenting between 2 and 5 years of age [37].

Despite considerable progress in treatment modalities and an overall survival rate approaching 80%, long-term survivors remain at substantial risk for disease relapse or progression of the primary neoplasm [37,38]. ALL is a heterogeneous disease, and its subtypes exhibit variable prognoses and relapse rates, often several years after initial remission [39]. Epidemiological data indicate the highest incidence in Hispanic children, whereas the lowest survival rates are observed among Black, Hispanic, and American Indian/Alaska Native populations [40]. Age at diagnosis is also a critical prognostic factor; infants (<1 year) exhibit markedly poorer outcomes (~34% survival) compared to children aged 1–9 years (~76%). Furthermore, sex-based disparities in survival have been documented, with female patients demonstrating superior outcomes relative to males, a phenomenon likely attributable to underlying genetic and chromosomal determinants [41–43].

Genomic instability plays a pivotal role in the pathogenesis of ALL, with multiple cytogenetic and molecular alterations influencing disease onset, progression, and therapeutic response [37]. Among the most frequently implicated genes are *IKZF1*, *CRLF2*, *PAX5*, and *FLT3*, each associated with distinct biological behaviour and clinical outcomes [37,39]. These genetic disruptions interfere with critical cellular pathways involved in haematopoiesis, tumour suppression, cell cycle regulation, and apoptosis. Notably, chromosomal abnormalities involving deletions on

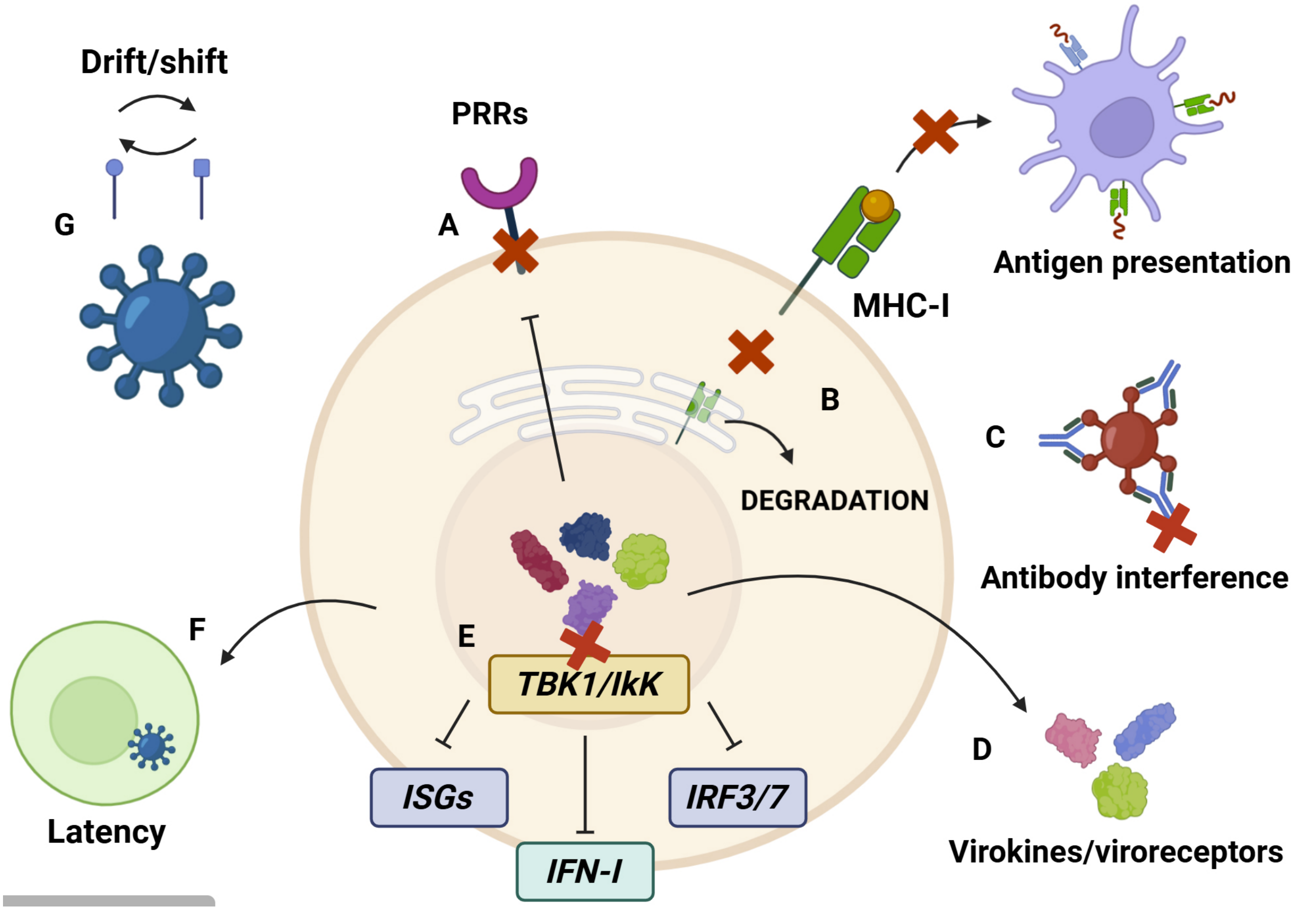

Fig. 1. Viral mechanisms of innate immune evasion. Pattern Recognition Receptors (PRRs) are blocked from recognising Pathogen-associated molecular patterns, and this prevents viral RNA/DNA from being identified. Two viral pathways are primarily involved in inhibiting the Molecular Histocompatibility Complex (MHC-I): the sequestration of MHC-I in the Endoplasmic Reticulum (ER) and hijacking the ER-associated degradation pathway (ERAD), which directs MHC-I molecules to the proteasome for degradation. Both pathways inhibit antigen presentation to immune cells such as natural killer (NK) cells. Antibody interference prevents antibodies from neutralising or clearing viral infections by binding to the Fc region and turning them ineffective. Some viruses can mimic host viral proteins to modulate key pathways to the virus's benefit for replication and latency in some cases. Generally, regulatory molecules like cytokines or receptors are encoded, known as virokines and viroreceptors. By blocking TBK1 and IKK, transcription factors such as IRF3 and IRF7, as well as *ISG* genes, are inhibited, downregulating interferon type I production, resulting in a low antiviral response in the cell. Latency is a specialised mechanism in which only a few genes and proteins are encoded for viral surveillance; the immune system cannot detect those foreign proteins, and elimination is inhibited. Antigen drift/shift refers to changes in surface antigens, particularly in influenza viruses, that enable them to evade immune detection or antiviral responses. Created in https://BioRender.com and accessed on 25th July 2025. Free BioRender plan licensed only for academic purposes.

the long arm of chromosome 6 (*6q*) are observed in 7–18% of ALL patients [41,44]. These large deletions often encompass genes essential for maintaining cellular homeostasis, including the *FOXO3A* gene. This transcription factor regulates apoptosis and proliferation and is considered a key candidate gene in ALL leukemogenesis [42,45,46].

The role of specific viruses in cancer development has long been established, and ongoing research is uncovering new viruses and their mechanisms associated with a higher risk during the first years of life. It is well known that certain viruses can induce cell transformation by disrupting the cell cycle and altering cyclin complexes, as these are essential quality controls that monitor cell integrity [47,48]. However, viral proteins have become a recent key focus of these disruptions because of their role in the inhibition of apoptosis, tumour suppressor genes, such as *Rb* or *p53*, activation of proto-oncogenes like *Myc* and *RAS*, generation of genomic instability promoting an uncontrolled cell growth and proliferation, and an immune response downregulation, which favour an oncogenic environment [32,48,49]—a topic explored in depth in the subsequent sections.

The Immune Response in the Tumour Microenvironment

Cancer development and progression are closely related to the host's innate and adaptive immune responses, which maintain homeostasis and regulate the dissemination of tumour cells through a mechanism known as immunosurveillance [50]. Antigen-presenting cells, such as dendritic cells and macrophages, detect abnormal antigens on cancerous cells via MHC-class I and target them for destruction through the action of NK cells and cytotoxic T lymphocytes [51]. By eliminating highly immunogenic tumour cells, cell surface antigens can be altered through specific mutations that facilitate immune evasion in a process known as immunoediting [52]. This allows cancerous cells with low immunogenicity or those that can suppress immunological effects to evade recognition by the immune system and proliferate, thereby breaking the equilibrium phase [50,53].

A tumoral microenvironment is also favoured by exacerbated inflammation resulting from injury, certain diseases, or viral infections [54]. Acute inflammation is a crucial component of the immune antiviral response, which induces the expression of specific genes with key roles in cell recruitment and viral clearance [54]. Most oncogenic viruses can disrupt inflammatory signalling pathways, such as the mitogen-activated protein kinase (*MAPK*), *NF-κB*, and *STAT3* pathways, causing chronic inflammation due to their persistence in the host and increasing the risk of gastric, colorectal, and hepatocellular carcinomas [55].

The role of inflammation in tumour development includes initiation, promotion, malignant conversion, invasion, and metastasis of mutated cells. The *NF-κB* pathway may act as a tumour suppressor; however, if aberrantly stimulated, it leads to the transcription of genes such as *BCLXL*, *BCL2*, *TNFA*, *IL6*, and *VEGF* that enhance cell survival, proliferation, angiogenesis, and metastasis [56]. Similarly, the constitutive activation of the *MAPK* pathway by *RAS* mutations leads to resistance to apoptosis-inducing drugs and uncontrolled cell growth [57]. *STAT3* plays a key role in inflammatory responses, the upregulation of anti-apoptotic genes, oncogenes, and angiogenesis. It is highly related to human cancer in cell transformation by the activation of the *Src* oncogene [58,59]. Chronic infections established in the host and characterised by persistent inflammation are major risk factors for cell transformation and oncogenesis.

Viral Immune Evasion Mechanisms

The host immune system has evolved and continues to adapt to recognise and respond to viral threats. In response, viruses have developed sophisticated strategies to evade immune detection and maintain their replication cycles. These immune evasion strategies include several tactics: molecular mimicry of host proteins, modulation of inflammatory and anti-inflammatory mediators such as cytokines and chemokines, disruption of cellular signalling pathways, suppression of humoral immune responses, interference with interferon signalling, and alteration of the expression of major histocompatibility complex (MHC) class I and II molecules. Most of these mechanisms are summarised in Table 1 (Ref. [8,12,24,30,55,57,60–83]).

Viral Protein Homologs

This mechanism, known as protein mimicry, is a common strategy employed by viruses to evade the immune system and hijack signalling pathways, including inflammation, cell growth, proliferation, apoptosis, and cell recognition to their benefit [3,69,84,85]. It constitutes one of the most prevalent viral immune evasion strategies, targeting specific host proteins involved primarily in cellular multiplication and inflammation, thereby establishing an optimal environment for virus surveillance and persistence [84,86]. The *Poxviridae* (*Monkeypox*, *Orf virus*, *Molluscum contagiosum*) and *Herpesviridae* (*EBV*, *CMV*, *HSV*, *Varicella Zoster*) families exhibit a higher rate of protein mimicry, as they can cause chronic infections [62]. Double-stranded DNA viruses also report elevated rates of mimicry, with *Herpesviruses* being more specific to humans. Overall, *Picornaviridae* and *Herpesviridae* proteins exhibit a multi-mimicking characteristic, which means they mimic a human motif scattered across multiple genes, conferring an advantage to modulate different pathways simultaneously, favouring not only efficient replication but also a long-lasting infection by evading innate and adaptive immune responses [62,87,88].

Herpesviruses are characterised by establishing lifelong infections in the host after primary infection, being able to switch between lytic and latent phases throughout their life cycle. Homologs are produced in both phases; however, latent proteins display more mimicry than lytic, suggesting that immune evasion may be more advantageous during latency [70,89,90]. This family has been associated with autoimmunity, with protein mimicry being one of the primary mechanisms that lead to cross-reactive responses, as it may take advantage of other acute infections to reactivate [31,91]. Reactivation periods also occur when immunosuppression or inflammatory processes are shown in the host, highlighting this downregulation as a possible factor of oncogene encoding and mutated cell surveillance [23,54,92–95]. Proteins like cytokines and chemokines are common targets that viruses mimic to exploit cellular machinery [60,96]. The strategies are primarily directed toward humoral responses, cellular responses, and effector functions, and they vary depending on the virus family and genome type (DNA or RNA) [60,87,97].

Viral homologs can exert similar effects, imitating the original host protein, e.g., EBV and CMV viruses encode a functional protein based on the *IL-10* human cytokine kno-

Table 1. Mechanisms of viral immune evasion and their effects on cellular function.

Mechanisms	Effect	References
Viral homologs	Mimics effector molecules and modifies cell pathways.	[60–63]
Inhibition of *JAK/STAT* pathway	Disrupted in ALL, promotes proliferation, survival, and resistance to apoptosis.	[30,64]
Inhibition of apoptosis	Immortalisation and dysregulation of the cell cycle.	[65,66]
Inhibition of MHC I and II	Degradation of MHC I and II and low immune responses.	[12,24,67]
TAP Inhibition	Prevents peptide binding to *TAP* in the cytosol and prevents peptide transport through the *TAP* pore.	[68,69]
Undergo latency	Dormancy within host cells and the production of viral proteins that manipulate cell machinery.	[70–72]
Disruption of the complement system	Impairment of antibody-mediated clearance.	[8,73]
Viral post-translational protein modifications (PTMs)	Non-recognition by the immune system using phosphorylation, methylation, and glycosylation.	[74,75]
Disruption of *RAS*, *MAPK*, *NF-κB*, and *STAT3* pathways	Manipulation of inflammation, cell proliferation, growth, apoptosis, proto-oncogenes, and gene expression, as well as chemotherapy resistance.	[55,57,76]
Disruption of *PI3K/AKT/mTOR* pathway	Present in ALL, enhances glucose metabolism, cell growth, and resistance to apoptosis.	[77,78]
Disruption of the *WNT/β-catenin* pathway	Promotes leukemic stem cell self-renewal, contributing to disease persistence and relapse.	[79,80]
p53 and Cell Cycle Checkpoints	Disruption in the cell cycle checkpoints lead to uncontrolled progression and resistance to apoptosis.	[81–83]

Table 2. Epigenetic mechanisms that are affected by viral proteins and their effects.

Epigenetic Mechanism	Effect	Virus	Viral Protein	References
DNA methylation and stimulation of methyl transferases	Affect gene regulation, chromatin structure and DNA wrapping.	*HPV* *Adenovirus*	*E7* *E1A*	[84,85,105,109,110]
Inhibition of *HAT* protein activity	Chromatin structure, transcription factors, and regulation of proteins that interact with DNA.	*EBV* *HPV*	*E6* *E7*	[111,112]
Modification of *DNMTs*	Cell cycle regulation, methylation patterns, stem cell function, gene silencing.	*EBV*	*LMP1*	[112,113]
Interaction with *p300* and *p400*	Gene expression, cell proliferation, differentiation, prevention of tumour growth.	*EBV* *HTLV-1* *Adenovirus*	*EBNA2* *Tax* *E1A*	[111,112]
Regulation of heterochromatin *H3K9me3*	Silencing lineage-inappropriate genes, haematopoiesis, is usually dysregulated in impaired cell differentiation.	*Adenovirus*	*E4ORF3*	[108,112,114]
Degradation of Rb and inducing histone acetylation changes	Alter cell cycle checkpoints.	hCMV	*UL82 (pp71)*	[115,116]
Dysregulation of *HDACs* (histone deacetylases)	Transcriptional repression of tumour suppressor genes.	HPV	*E7*	[107,117,118]
Mutations in *KDM6A* (*UTX*)	Affect demethylation of *H3K27me3*, promoting leukemogenesis.	EBV HTLV-1 HPV	*EBNA, LMP1* *Tax* *E6, E7*	[119–121]
Rearrangement of *KMT2A* alters histone *H3K4* methylation	Promotes the transcription of oncogenic targets such as *HOXA*.	EBV HPV HTLV-1 HBV	*EBNA1, LMP1* *E6, E7* *Tax* *HBx*	[121–123]
Modulation of chromatin structure	Interaction of *HDAC1/2* and *uDNMT* activity and an increase in DNA methylation.	hCMV	*IE86 and UL111A*	[116,121,124]

wn as viral *IL-10*, which manipulates the anti-inflammatory response, similar to the viral homolog of protein *NFKB-I* encoded by *Vaccinia virus* that reduces stimulation of *NF-κB*-regulated chemokine genes *CXCL10* and *CCL2*, downregulating in both cases immune cell recruitment and effector antiviral responses [76,98,99].

Disruption of Antigen Presentation Pathways

The immune system plays a critical role in identifying virus-infected cells by presenting oligopeptides derived from viral proteins on the cell surface. Antigen-presenting cells, such as dendritic cells and macrophages, express major histocompatibility complex (MHC) on their surface, which allows them to bind to T cells [67,100]. The MHC is classified into two distinct types—class I and class II—based on the cellular origin of the antigen, whether it is intracellular or extracellular. MHC class I molecules form a heterotrimeric complex composed of *β2-microglobulin* (*β2m*), a polymorphic heavy chain, and a peptide fragment of pathogenic origin [100]. Peptides presented via MHC class I are predominantly derived from cytosolic proteins and are recognised by CD8+ cytotoxic T lymphocytes, which are essential for the targeted elimination of infected or neoplastic cells [100,101]. To evade immune surveillance, certain viruses have evolved mechanisms to disrupt this antigen presentation pathway, often by targeting MHC class I molecules for retention and degradation in the endoplasmic reticulum (ER) through ER-associated degradation (ERAD). This interference effectively impairs antigen presentation, thereby facilitating the persistence and propagation of infected cells [12,24,67].

Several viral proteins have been shown to directly impair the synthesis, stability, and surface expression of major histocompatibility complex class I (MHC I) molecules, thereby enhancing viral immune evasion and promoting viral replication and persistence within the host [12,24,67]. A well-documented example is Human Cytomegalovirus (hCMV), which encodes the immunoevasins *US2* and *US11*. These proteins interfere with the proper association of *β2-microglobulin* with the MHC I heavy chain, targeting the complex for proteasomal degradation and ultimately resulting in diminished MHC I surface presentation [102,103]. Another prominent mechanism employed by viruses involves the expression of peptide mimics that inhibit the transporter associated with antigen processing (*TAP*), a heterodimeric ATP-binding cassette (ABC) transporter composed of *TAP1* and *TAP2* subunits [68,69,104]. Under normal physiological conditions, *TAP* mediates the translocation of antigenic peptides into the endoplasmic reticulum (ER), where they are loaded onto MHC I molecules for subsequent presentation to cytotoxic $CD8^+$ T lymphocytes [68,69]. Inhibiting this pathway represents a key strategy by which viruses subvert immune surveillance (Fig. 2).

Viral Alterations in Epigenetic Regulatory Mechanisms

Recent evidence suggests that epigenetic processes play a crucial role in the viral life cycle, actively participating in the transmission, persistence, and maintenance of the infection [105,106]. The mechanisms involved are DNA methylation, histone modification, and microRNA modification, which confer advantages for immune evasion and viral persistence [85,106]. Histone modifications, chromatin remodelling, DNA methylation, and non-coding RNA are components of cellular regulatory networks, and their disruption may lead to gene manipulation, pathway disruption and mutations [105,107] (Table 2, Ref. [84,85,105,107–124]). For example, Influenza A virus subtype *H3N2* encodes the *NS1* protein, and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) encodes *ORF8*; both proteins contain short peptide sequences that mimic host histones (Fig. 3). Another example is gene hypermethylation, which has been linked to the suppression of antiviral genes, thereby compromising the host's immunity and facilitating viral persistence [21,107].

After viral entry, epigenetic mechanisms can help some viral families undergo latency. DNA methylation, histone modifications and non-coding RNAs can silence viral chromatin and limit transcription processes. Some proteins, known as repressors (*HFH-3*, *v-Myb*, *E2F*, *Maf*, and *AP1*), can disrupt the host transcription pathway and contribute to latency [108].

In *Herpesvirus* like EBV, these mechanisms can also regulate gene expression during latency periods or in chronic infections and may regulate viral reactivation to lytic infection [105]. Mimicry-targeted proteins, including histones, chemokines, and cytokines, to disrupt the host chromatin architecture, which is crucial for regulating DNA-dependent cellular processes, such as transcription. By replacing host histones within nucleosomes, viruses interfere with host factor interactions involving histone tails, thereby subverting the host's immune defences [105,109,110].

Pattern Recognition Receptors (PRRs) and Viral Evasion

Pattern recognition receptor signalling (PRRs) is essential in the interaction between innate and adaptive immune responses, initiating defence mechanisms and maintaining host homeostasis [125]. These receptors can sense viral pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), playing a crucial role in activating signalling pathways that modulate inflammation and antiviral responses, as well as eliminating premalignant cells [125,126]. It is one of the mechanisms by which viruses disrupt the immune system and contribute to cancer development. The classification of PRRs depends on their location in the cell. Membrane receptors include *Toll-like receptors* (*TLRs*) and *C-*

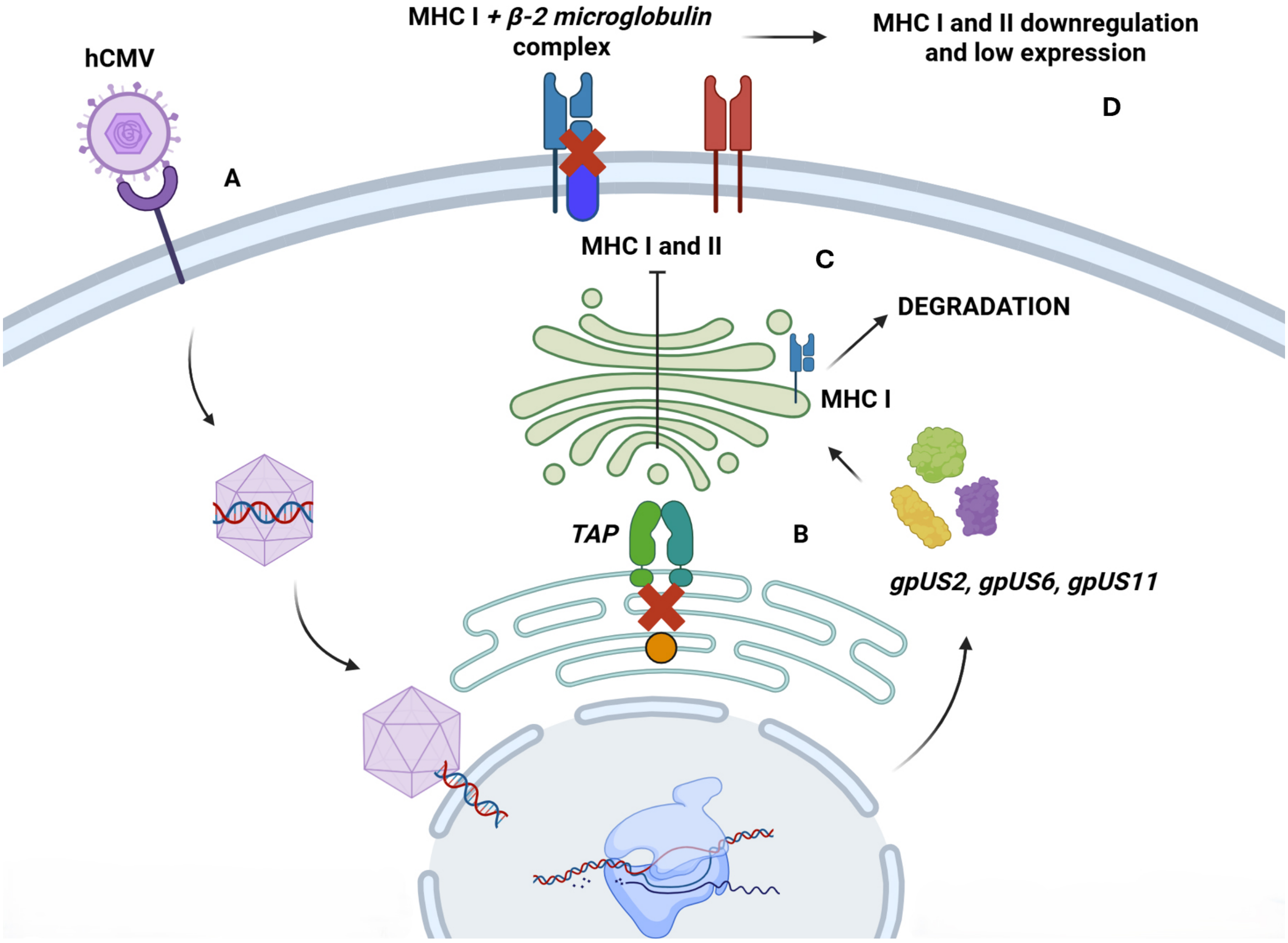

Fig. 2. Molecular histocompatibility complexes (MHC) I and II disruption by human cytomegalovirus (hCMV). (A) Cytomegalovirus enters the cell, and the capsid releases viral DNA in the nucleus. (B) The gpUS2, gpUS6, and gpUS11 proteins are encoded and inhibit the ABC transporter TAP function, resulting in downregulation of MHC I and reduced surface expression. (C) These proteins also induce the degradation of MHC I in the endoplasmic reticulum (ER). (D) As a result, immune responses are reduced, and this favours viral surveillance. Created in https://BioRender.com and accessed on 31st May 2025. Free BioRender plan licensed only for academic purposes.

type lectin receptors (*CLRs*). Cytosolic receptors include *retinoic acid-inducible gene I* (*RIG-I*) (*RLRs*), *nucleotide-binding oligomerisation domain* (*NOD*)*-like receptors*, *absent in melanoma 2* (*AIM2*)*-like receptors* (*ALRs*) and *cyclic guanosine monophosphate* (*GMP*)*-adenosine monophosphate* (*AMP*) *synthase* (*cGAS*) and adaptor proteins that lead to signalling, including *MAVS* and *STING* [125,126].

RNA viruses replicate in the cytoplasm of the cell and are detected by *RIG-I* and *MDA5*, whereas DNA viruses replicate in the nucleus and are recognised by *cGAS* and *IFI16* [127]. By ligand-receptor binding, the production of proinflammatory cytokines and *type I interferon* (*IFN*) is stimulated and regulated. To date, 10 human *TLRs* have been described and are key targets for viruses to evade the immune system [128]. The *TLR9* receptor, known to trigger a signalling cascade that produces pro-inflammatory molecules and activates immune cells, is targeted by viruses like EBV, whose *LMP1* oncoprotein downregulates its transcription and affects the *NF-κB* pathway [126,129]. As a result, immune genes are not activated correctly, leading to inadequate immune responses. Receptors *TLR3* and *TLR4* play a crucial role in detecting double-stranded RNA (dsRNA) viruses and bacteria; they are altered by infection, underscoring the impact of human oncogenic viruses (HTLV-1, KSHV, HSV), which results in reduced receptor mRNA levels [126,129].

Not only can immunologic responses be compromised by the disruption of these PRRs and their pathways, but they've also recently been suggested as risk factors for oncogenesis [130]. As inflammation promoters and regulators of excessive responses during infection, the dysregulation of PRRs due to viral protein influence creates a favourable microenvironment for tumour formation. It helps pre-malignant clones to proliferate and evade elimination [130,131].

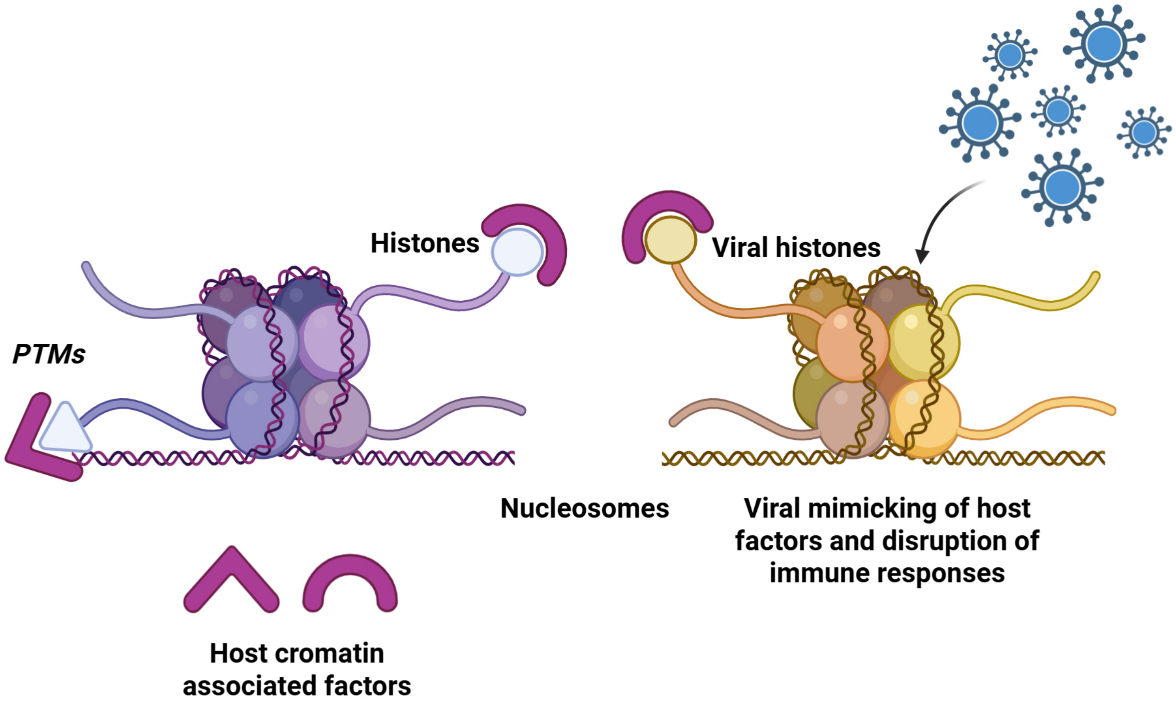

Fig. 3. Host gene regulation via epigenetic mechanisms manipulated by viruses. Certain viruses can mimic short linear motifs and regions of host histones that bind to host factors, thereby controlling cellular machinery and processes, including cell growth, proliferation, and immune responses, during infection. Created in https://BioRender.com and accessed on 31st May 2025. Free BioRender plan licensed only for academic purposes.

Viral Latency and Immune Evasion

Latency is a viral mechanism related to immune evasion that allows the establishment of a lifelong infection in the host [132,133]. *Retroviruses*, *Poxviruses* and *Herpesviruses* are viral families characterised by a dormant or quiescent state; which means that the viral genome persists in infected cells, but there is no active protein production [73,132]. To maintain viral DNA integrity, it remains as an episome and can reactivate under proper conditions in a process known as "reversibility" [73,132]. HIV and all human *herpesviruses* (HSV I and II, Varicella zoster, Epstein-Barr, HHV-6 and 7, Kaposi's sarcoma-associated herpesvirus and cytomegalovirus) enter this phase following the primary infection [73,89,133]. The set of specialised proteins produced during latency is related to immune evasion, reactivation sensing and viral surveillance [70–72].

Diverse pathologies have been recently associated with the viral latent stage; however, cancer derived from chronic inflammation and pathway signalling disruption during infection, as well as viral protein encoding, has garnered considerable interest [134]. The outcomes of viral latency vary among viral families, but a dynamic equilibrium between the host's immune responses and the virus's persistence is necessary for viral establishment and surveillance. A disequilibrium can lead to severe diseases, such as autoimmunity and oncogenesis [23,48,61,92,135].

Members of the *Herpesviridae* family, such as EBV, HSV, and hCMV, undergo latency, which is not only described as a mechanism to evade antiviral responses but is also recently linked to tumorigenesis. It is known that only a few genes and proteins are encoded during this phase to maintain the viral genome without being recognised by the immune surveillance [136,137]. Nevertheless, the functions of latency viral proteins and pathways remain under research and might represent essential targets for treatments and therapies.

Herpesviruses: Strategic Evasion of Host Immunity

As previously mentioned, the *Herpesviridae* family orchestrates its replication cycle through alternating lytic and latent phases, facilitating immune evasion and the establishment of persistent infections after primary exposure [70,89,138]. Reactivation events, often triggered by immunosuppression or inflammatory stimuli, have been well documented. The lytic phase involves the production of active virions and the expression of numerous proteins essential for viral genome replication and virion assembly [137]. In contrast, the latent phase is characterised by an absence of detectable virions due to minimal viral replication and restricted protein expression, the functions of which remain largely undefined. Nonetheless, these latent proteins are implicated in immune evasion and molecular mimicry, thereby promoting viral persistence and successful infection [89,90,133,138].

Human cytomegalovirus (HCMV), a *beta-herpesvirus*, is recognised as the leading cause of congenital infections worldwide. Seroprevalence studies indicate that approximately 90% of adults harbour latent HCMV, with vertical transmission occurring in roughly 10% of neonates via transplacental, perinatal, or postnatal routes, including breastfeeding [139,140]. While infections are generally asymptomatic in immunocompetent individuals, severe manifestations may occur in immunocompromised hosts [72,141,142]. Structurally, HCMV possesses an icosahedral proteinaceous nucleocapsid encapsulating a ~230 kb double-stranded DNA genome, surrounded by a tegument and an outer lipid bilayer envelope containing multiple glycoprotein complexes critical for host cell attachment and entry [138].

Proteins integral to viral replication and immune modulation are expressed during both lytic and latent phases. HCMV employs diverse immune evasion mechanisms, including the disruption of antigen presentation via major histocompatibility complex (MHC) class I and II molecules [72,140,142,143]. Additionally, HCMV modulates host chemokine and cytokine expression profiles to skew immune responses toward an anti-inflammatory phenotype and suppress the activation of immune cells. These strategies facilitate low-level viral replication and the establishment of viral reservoirs within specific host cell populations [136,143] (Fig. 4).

Viral gene expression is temporally regulated into three kinetic classes: immediate-early, early, and late. During the lytic cycle, viral proteins are sequentially expressed according to these phases, whereas latency is characterised by minimal protein expression. The molecular mechanisms governing latency maintenance and reactivation remain incompletely understood. Notably, latency reservoirs predominantly reside within cells of the myeloid lineage [144,145].

Role of Viral Immune Evasion in Childhood Cancer

Although cancer has multiple origins, it has been recently suggested that these origins may be linked to viral infections [23,48,146]. Promoters of this disease may not act directly on wild-type cells, but rather on preneoplastic cells, which can progress to full malignancy [147]. hCMV can trigger inflammation processes observed in other pathogens associated with cancer [95,148,149]. Evidence suggests that human cytomegalovirus (hCMV) infection and viral genome expression are detected in human malignancies through the induction of cytokines and other modulators, which may contribute to alterations in the cellular microenvironment and tumour development [150,151]. Additionally, proteins involved in immune evasion that are expressed during latency can help cancer cells evade the immune system [152,153]. Infection during pregnancy or delivery can alter the newborn's cytokine and chemokine profiles, leading to a deficient immune response and potentially acting as a promoter in childhood hematologic malignancies and cancer development [139,154–156] (Fig. 5).

Members of the *Herpesviridae* family have been described as a direct contributor to oncogenesis [94,138]. Latency proteins, such as *LMP-1* from EBV, are suggested to upregulate interleukin and gene expression (*BCL-2*, *MCL-1*, and *A20*) related to protecting infected B cells and causing a failure in *p53*-mediated apoptotic responses [70,89,108,133,157]. The activation of anti-apoptotic factors, such as nuclear factor kappa (NF-κB) and *STAT-1*, interferes with the cell cycle and metabolism, affecting host pathways and proteins that regulate cell growth and proliferation, which can lead to cancer development [55,56,58,158–161]. Other viruses have been proposed as potential cancer sources, but their role is still under research. For example, human cytomegalovirus (hCMV) has lately been linked to infant leukaemia [99,162–165]. The viral mechanisms remain unknown; however, this virus may induce cell transformation during infection and latency through specific protein-encoding mechanisms (Fig. 6) [148,153,166].

Viruses play an essential role in evolution due to their capacity to adapt to their hosts and develop specialised mechanisms to remain within the host and control cell machinery, thereby improving and establishing longer infections. Viruses often influence autoimmune diseases and cancer. However, their function is still unknown; the proteins encoded by these viruses could represent a primary target for therapies and a better understanding of the development of these diseases.

Discussion

As viruses rely on cellular machinery to replicate, the mechanisms developed to control cell signalling pathways and reprogram proliferation, growth, differentiation, apoptosis and immune responses are wide. According to Lu *et al.* (2024) [167] and Mattoscio *et al.* (2013) [74], protein encoding represents one of the most frequent mechanisms used by viruses to establish a successful infection during replication and spread. In specific viral families, it also participates in latency to evade host immunity [74,167].

The viral targets correspond to the host's first line of defence, elements of the innate immunity such as the pattern recognition receptors (PRRs), that recognise pathogen-associated molecular patterns (PAMPs) for viral clearance. As reported by Lu *et al.* 2024 [167]; Li *et al.* 2024 [168] and Bowie and Unterholzner 2008 [169], the variety of receptors, including *Toll-like receptors* (*TLRs*), *RIG-I-like receptors* (*RLRs*), and *NOD-like receptors* (*NLRs*), can control many of the key pathways that promote antiviral responses; however, the subversion of these signalling pathways, such as *NF-κB*, *MAPK*, *cGAS/STING*, and *JAK/STAT*, not only results in low immunologic responses but also promotes an inflammatory microenvironment and genomic instability. Examples of these effects are shown in viruses and

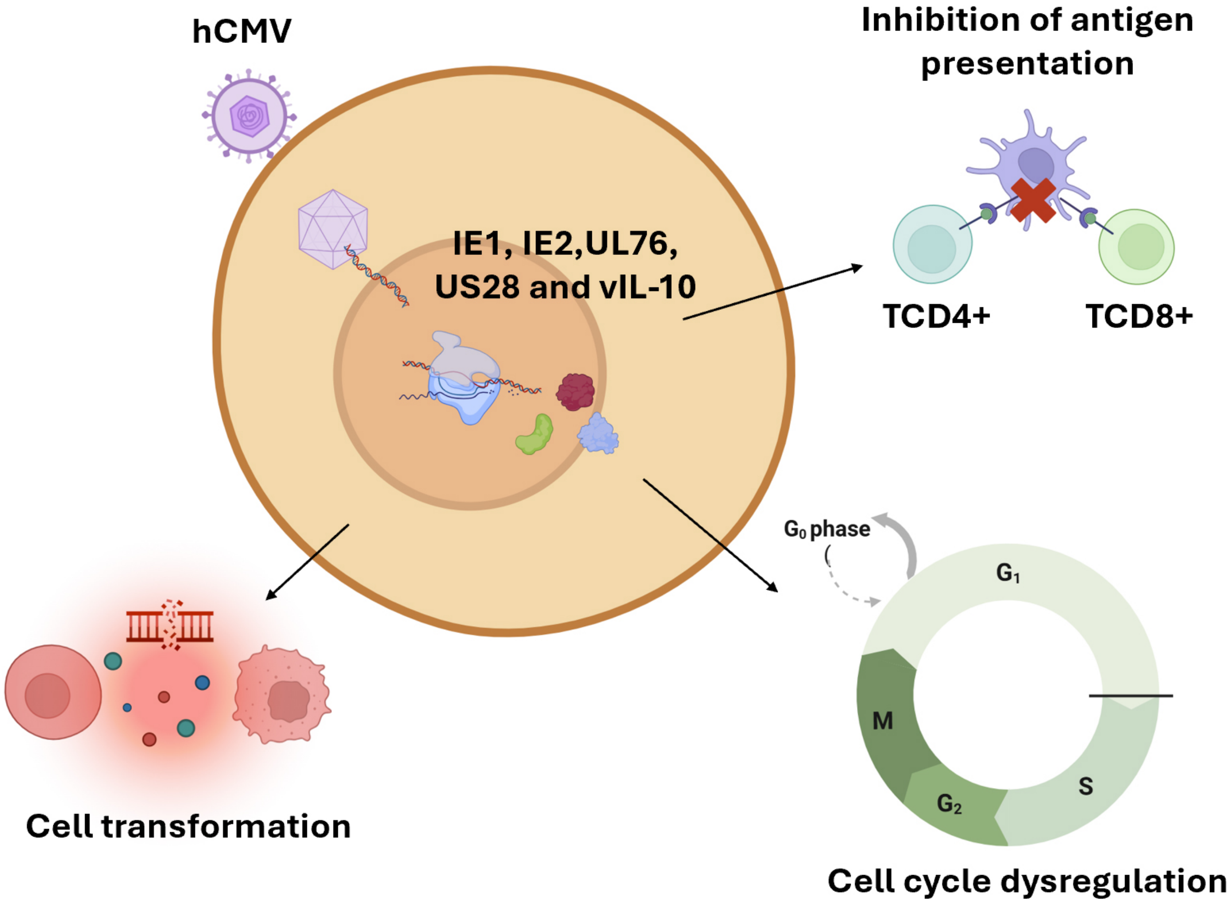

Fig. 4. Human cytomegalovirus (hCMV) encodes a few proteins that mimic the host. The viral inhibitor of caspase-8 activation (vICA) is encoded by the UL36 gene and plays a role in protecting infected cells from apoptosis. It interacts with TNFR1 and FAS/CD95 receptors, resulting in the inactivation of caspase 8. UL144 protein acts as a competitor of TNFR, which typically binds to ligands such as LIGHT, LTα and BTLA to inhibit the activation of B and T cells; it also activates NF-κB transcription of the chemokine *CCL22* gene, which blocks immune responses in T cells. Viral proteins UL16, UL18, and UL40 are responsible for innate immune evasion by "hiding" infected cells from detection by natural killer cells (NK). The UL111A gene encodes a homolog to the human cytokine IL-10 that activates the STAT3 transcription factor, exerting immunosuppressive effects by inhibiting the expression of MHC I and II in CD4+ and CD8+ T cells. Viral IL-10 (vIL-10) also contributes to the extracellular matrix degradation by downregulating the expression of cell adhesion genes. This allows tumour cells to disseminate, increasing their metastatic and invasive phenotype. By downregulating inflammation, the immune response is less efficient in eliminating cancer cells, promoting tumour formation. vIL-10, IE1, and IE2 proteins are suggested to bind to major tumour suppressors such as p53 and Rb by the phosphatidylinositol 3-kinase/serine/threonine kinase (PI3K/AKT) pathway inhibiting apoptosis or sequestering these proteins in the cytosol. Created in https://BioRender.com and accessed on 31st May 2025. Free BioRender plan licensed only for academic purposes.

their proteins like VACV (*E3L* and *A52R*), HTLV-1 (*Tax* and *HB2*), EBV (*LMP1*, *LMP2*, *EBNA1* and *EBNA2*), HBV (*HBx*, *HBs Ag*), HCV (*Core* and *NS1-5*), EBOV (*VP35*) and Influenza A virus (*NS1*), which can affect different elements such as (*TLR*, *PKR*, *IRF*, and *RIG-I*) contributing to viral survival and modifying cytokine and chemokine production, leading to a wide variety of possible outcomes [167–169].

Typically, in the early stage of infection, a pro-inflammatory environment predominates, activating immune cells and facilitating antigen recognition; however, the disruption of innate immunity elements may cause chronic inflammation that leads to oxidative stress and DNA damage, thereby increasing the risk of mutations and cell transformation. Conversely, in the late stage of infection, anti-inflammatory cytokines modulate inflammation and reduce tissular damage; nevertheless, Ruvalcaba *et al.* 2025 [99]; Veld *et al.* 2024 [170] and Rojas *et al.* 2017 [98] suggest that a continuous production of these elements, like *IL-10*, can favour viral persistence by the interaction/inhibition of host proteins such as *IRAK2*, *TRAF6*, *IKKs*, *MAVS*, *TBK1*, *c-Myc*, *IRF3*/*7*and *IL-8* related to *ISGs and* interferons [167–169]. Viruses such as *ORF Parapoxvirus*, EBV and hCMV encode homologs of this cy-

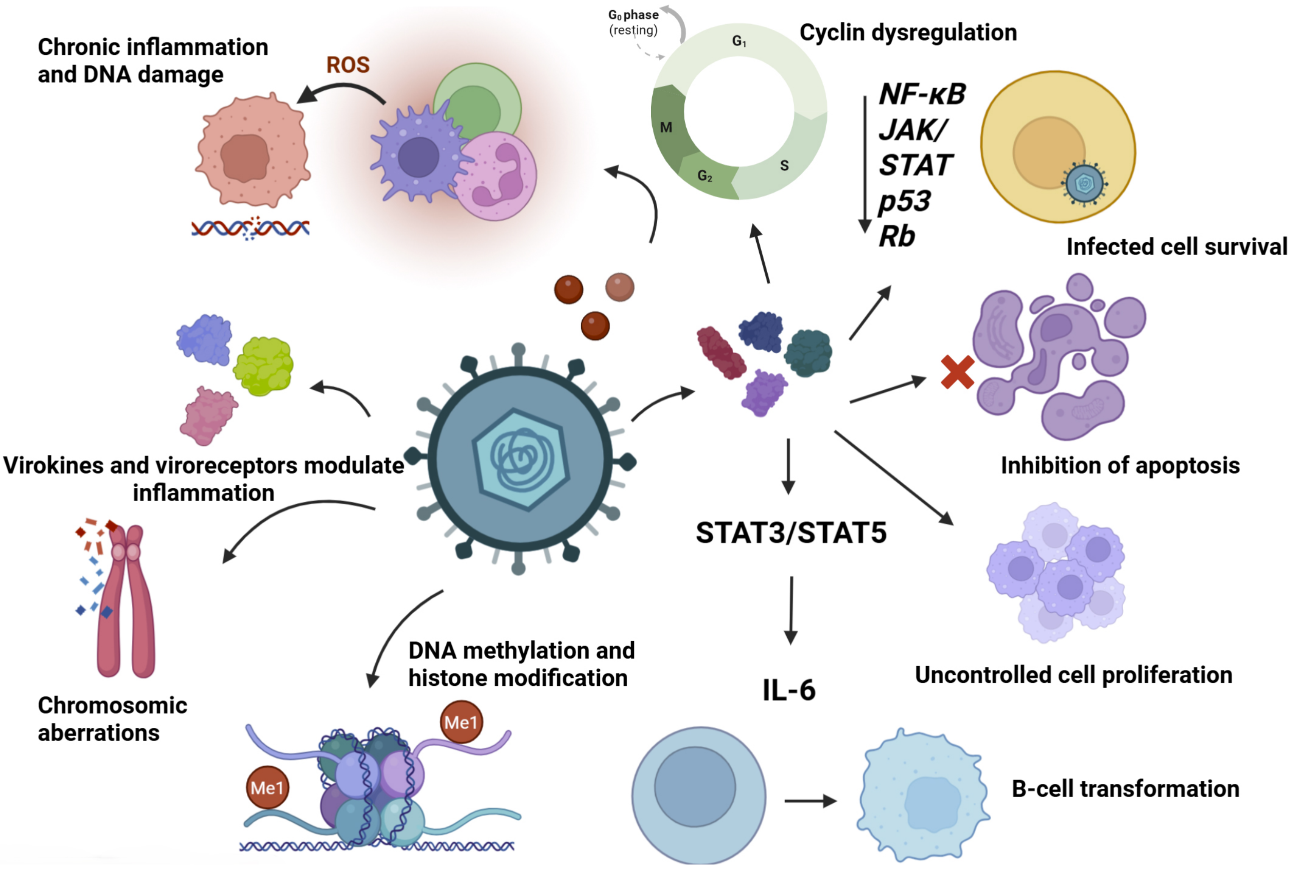

Fig. 5. Viral mechanisms involved in paediatric oncogenesis. During infection, a diverse array of proteins is encoded to modulate multiple cellular pathways. Proinflammatory cytokines induce the release of active oxygen species (ROS), leading to DNA damage. Virokines and viroreceptors are produced to modulate inflammation and viral surveillance. Some viruses can integrate their DNA genome into the host, disrupting tumour suppressor genes or activating oncogenes. The alteration of epigenetic factors in the host cell—DNA methylation, histone modification, and non-coding RNA—promotes cell transformation and cancer. Viral proteins can activate factors such as STAT3/5, which upregulate pro-inflammatory elements like IL-6 and may lead to B-cell transformation. Moreover, various pathways, including NF-κB, JAK/STAT, and tumour-suppressor genes such as p53 and Rb, contribute to the surveillance of infected cells, the inhibition of uncontrolled proliferation, and the promotion of apoptosis. All these mechanisms lead to pro-oncogenic environments and favour children's oncogenesis, highlighting early infections, cytokines and chemokines profiles. Created in https://BioRender.com and accessed on 25th July 2025. Free BioRender plan licensed only for academic purposes.

tokine during lytic and latent phases; moreover, the authors emphasise that overexpression of *IL-10* can also contribute to immunosuppression and the dissemination and survival of pre-malignant clones [98,99,170].

During infection, many other viruses exploit the cell's epigenetic machinery through mechanisms such as DNA methylation, histone modifications, and chromatin remodelling, all of which play critical roles in regulating immune responses and viral stability. Saha *et al.* 2025 [106]; Rehman *et al.* 2023 [105]; Locatelli and Faure-Dupuy 2023 [21] and Lieberman 2016 [132], described that epigenetic changes can favour post-translational protein modifications, viral surveillance, and modulate innate and adaptive immunity. By altering DNA methylation, the pathogen recognition capacity may be delayed, and IFN genes can be silenced. Histone modifications can also affect antigen presentation by downregulating molecules such as MHC-I. Furthermore, antitumor genes like p53 and Rb can be suppressed, which favours a pro-oncogenic microenvironment. This has sparked a new research interest, as viral infections have been linked to the development of oncogenesis. Viruses such as SARS-CoV-2, Influenza A, EBV, KSHV, VPH, HSV-1, and hCMV can suppress the apoptotic pathway, control cytokine production, and dysregulate the cell cycle, changes that can persist for years and are considered cancer hallmarks [105,106,132].

As previously mentioned, the MHC-I pathway targets infected cells for elimination by presenting viral antigens to CD8+ T cells. The inhibition of proteolytic activity, due to the influence of viruses such as EBV (via EBNA1) and KSHV (via LANA1), prevents the degradation of proteins, thereby avoiding their presentation by MHC-I to CTLs. Wu

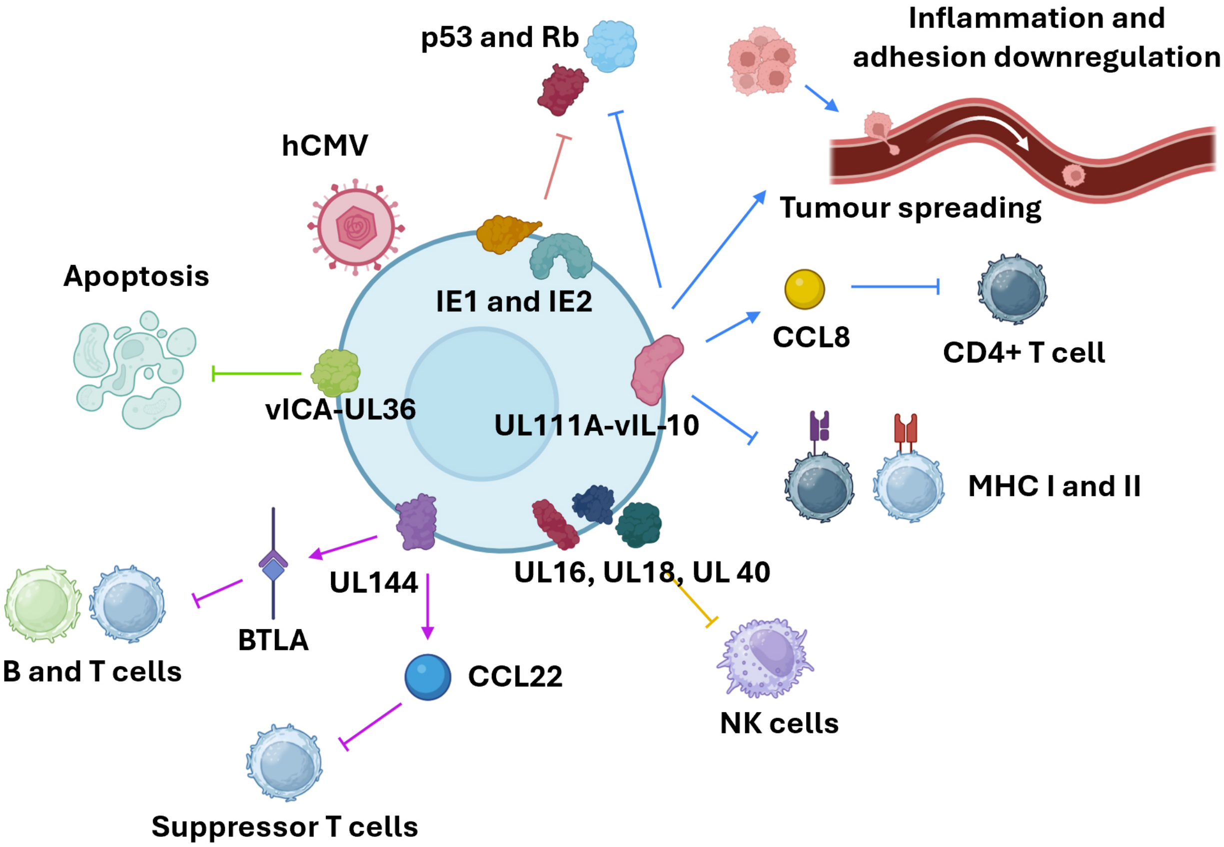

Fig. 6. Human cytomegalovirus protein vIL-10 mimics host IL-10 to regulate NF-κB and JAK/STAT pathways. Both play a significant role in cell surveillance, the cell cycle and the regulation of T cells and inflammation. Viral latency proteins, such as IE1, IE2, UL76, US28, and vIL-10, disrupt these mechanisms by inducing the degradation of major histocompatibility complexes (MHC) and inhibiting antigen presentation to CD4+ and CD8+ T cells. The effectiveness in identifying pre-leukemic malignant clones is reduced, increasing the risk of developing leukaemia. The alteration of cyclin expression and the ability to manipulate the cell cycle are also mechanisms modulated by viral proteins that lead to cell immortality and uncontrolled, abnormal cell division. Another sequel is cell transformation by viral manipulation of inflammatory factors such as cytokines and chemokines. During infection, molecular profiles are modified, which affects cell activation and the surrounding microenvironment. Exacerbated inflammation favours genetic and epigenetic damage and mutation, leading to a cancerous phenotype. B and T cell precursors are affected in the bone marrow, triggering leukaemia. Created in https://BioRender.com and accessed on 31st May 2025. Free BioRender plan licensed only for academic purposes.

et al. 2025 [24]; Hansen and Bouvier 2009 [171] and Petersen *et al.* 2003 [12] highlight the role of the TAP receptor formed by the subunits TAP1 and TAP2, which is targeted by viruses, as it forms a pore across the ER, allowing peptide translocation. HSV (*ICP47*), EBV (*BNLF2a*) and hCMV (*US6*) block peptide binding to the cytoplasmic face of the TAP receptor, limiting peptide supply and impairing MHC-I maturation. Tapasin pathway is also part of the stability of MHC-I, and viral proteins from adenoviruses (*E3-19K*), CPXV (*CPXV203*) and hCMV (*US3*) cause MHC-I to be retained in the ER, downregulating its expression. The mechanisms involve direct binding to tapasin, inhibiting tapasin's ability to bridge TAP to MHC-I, and molecular mimicry of the TAP binding site. As a result, MHC-I can be induced to degradation by ERAD (Inducers of ER-associated degradation), a process involving viruses and proteins such as KSHV (*K3/5*) and hCMV (*US2* and *US11*), which associate with MHC-I heavy chains and induce rapid endocytosis and lysosomal degradation of the complex [12,24,103,171].

All described mechanisms enable viruses to evade the host's immune responses, allowing them to survive and replicate. However, in some cases, they are also linked to cancer development, as they lead to a weakened immune response, which permits malignant clones to spread and proliferate, and the accumulation of genetic aberrations and mutations that lead to cell transformation and the sequestration/inhibition of anti-tumoral genes. This is supported by Bautista and Lopez-Cortes 2025 [112]; Herbein 2024 [148]; Dong *et al.* 2024 [107]; Guven-Maiorov *et al.* 2019 [61]; Colotta *et al.* 2009 [172] and Smyth *et al.* 2006 [50]. Oncogenic viruses establish lifelong infections in the host and "hide" within specific cells to continue producing a limited number of genes, thereby surviving and evading detection. They are identified to express certain hallmarks that relate them to direct tumorigenesis; however, some non-oncogenic viruses exhibit many of those hallmarks and have been proposed as possible new oncoviruses due to their strong correlation, still under research, with illnesses such as leukaemia [50,61,107,112,148,172].

The aetiology of cancer is multifactorial, encompassing environmental, genetic, age-related, and ethnic factors; however, two essential origins are described by many authors, viral and non-viral. According to recent studies, approximately 15% to 20% of cases are associated with viral infections, and the role of viruses in these cases has been a topic of ongoing discussion. The understanding of viral cancer development is based on the study of oncogenic viruses to identify the cellular networks involved and the progress of molecular-targeted therapies [146]. Only seven viruses have been officially recognised to present all or most of the disease hallmarks. The discovery of oncogenes, tumour suppressors, and the integration of viral genomes into the host genome suggests that viruses can contribute to different steps of carcinogenesis and are key factors in the development of certain malignancies.

The emergence of malignancies in children related to infections is the subject of recent research. Immunological mechanisms and responses are crucial to understanding how certain viruses pose a significant risk of cancer development during childhood. Latency in chronic infections is mainly related to the spread of malignant clones, as viral proteins manipulate the immune responses and modulate tumour-suppressor genes. The most common cancer in infants is acute lymphoblastic leukaemia, present in around 75% of all childhood leukaemia cases.

Regarding viral infections, their contribution to leukaemia can be direct through cell transformation or indirect through abnormal immunological responses or genetic alterations. Even though many viral families are proposed as causal agents, such as *Retroviridae*, *Poxviridae*, and *Herpesviridae*, the latter stands out for the ability to interfere with the host cell cycle checkpoints (cyclins and CDKs), apoptosis pathways, and DNA repair, considered essential hallmarks in cancer development according to Contreras *et al.* 2024 [92]; de Marte *et al.* 2020 [135] and Morales-Sánchez and Fuentes-Pananá 2014 [48]. EBV (*EBNA3C* and *EBNA-LP*) interact with *Rb* and releases *E2F*, which favours transition from G1 to S in the cell cycle. KSHV (*v-cyclin*) activates CDK-6 and transitions from G1 to S, HSV-1/2 (ICP0 and ICP27) interfere with p53 and disrupt DNA damage sensing, and hCMV (*IE86*) inactivates Rb and promotes transition to S phase. Choi and Lee 2024 [173]; Panda *et al.* 2023 [174] and Mesri *et al.* 2010 [175] determine these viruses' role in the loss of cell cycle control, leading to uncontrolled growth and proliferation, which are related to oncogenesis through cell transformation and a failure to eliminate abnormal cells.

Herpesviruses are also suggested to be a causal agent of leukaemia. Although several of its members are already officially considered oncoviruses, the establishment of chronic infection by all members of the family, along with the similarity of their mechanisms to evade the host immune response, places them as risk factors. An example of this is hCMV, as many recent studies have found viral DNA in tumours and in utero during pregnancy, linking the infection to a higher risk of childhood cancer development. Yu *et al.* 2023 [151]; Wiemels *et al.* 2019 [155]; Cobbs *et al.* 2019 [176]; Francis *et al.* 2017 [162] describe the possibility that infection in the early stages of pregnancy or during the first years of life increases the risk of developing ALL in children under 15 years of age. Moreover, alterations in cytokine and chemokine profiles have been noted during CMV infections, particularly in pregnant mothers, which may facilitate the dissemination of pre-leukemic clones in offspring, as they are not eliminated by immune vigilance, and potentially contribute to the emergence of leukaemia. The debate among authors remains centred on whether the virus has a direct or indirect influence on cancer development, as it has been observed that the virus cannot induce cell transformation in human cells; however, it can in rodent cells. Additionally, the involvement of hCMV has been proposed to encompass various mechanisms at different stages of infection that may favour an oncogenic state. Compared to other *Herpesviruses*, hCMV V infects undifferentiated cells of the myeloid lineage, such as CD34+ hematopoietic progenitor cells (HPCs), the infection becomes latent and may downregulate inflammatory mediators and antiviral responses by overexpressing *IL-10,* through a homolog (*vIL-10*), as well as inhibiting *p14ARF* and *p16INK4* proteins, which control tumour suppression through *p53* and *Rb*. The latency-associated proteins *IE1*, *IE2*, *UL76*, *US28*, and *vIL-10* may also interfere with the expression of cyclin-dependent kinases, RNA transcription, post-translational protein modifications, and proteolytic degradation pathways. Consequently, these genes and proteins may halt the cell cycle before the synthesis of host DNA (S phase) and disrupt critical checkpoints that typically prevent errors in DNA during cell division, thereby promoting the proliferation and dissemination of pre-leukemic clones. Finally, hCMV infection can also disrupt JAK/STAT and NF-κB signalling pathways; as a result, proliferation and apoptosis resistance are increased [151,155,162,176].

A large part of the aetiology of childhood cancer remains unknown. However, infections of certain viral families represent a higher risk factor in addition to genetic and environmental factors. The relationship between immune evasion mechanisms developed by viruses, the proteins involved, and the different stages of infection is a key element for developing new therapies and preventing cancer, particularly in cases of early infection. Moreover, understanding the biology and interactions of oncogenic viruses can represent a significant contribution to infection prevention in both mothers and children, reducing the frequency of such infections during pregnancy and the first years of life.

Conclusions

The link between virus-induced cancers and immune evasion mechanisms is not to be overlooked. Viral proteins that evade immune responses significantly disrupt host cellular pathways, thereby contributing to the development of autoimmune conditions and malignancies. Although human cytomegalovirus (hCMV) has not yet been fully classified as an oncovirus, it serves as a prime example of a virus with diverse evasion strategies throughout its infection cycle. This adaptability underscores its potential role in oncogenesis, especially in childhood acute lymphoblastic leukaemia (ALL), which remains a leading cause of cancer-related mortality worldwide. The detection of viral DNA in leukemic samples lends support to the hypothesis that hCMV may act as a significant oncogenic factor. Continued research into immune evasion mechanisms and the role of latency proteins is crucial for developing innovative therapeutic and preventive strategies against virus-related cancers.

Availability of Data and Materials

Not applicable.

Author Contributions

PRH, ARL, and JAG conceived the study, designed the framework, and drafted the initial manuscript. JCNE, MMR, EJH, JMMA, SPMD, JXC, SAO, and ACC performed the literature search and data collection, and provided critical revision of the manuscript for important intellectual content. All authors read and approved the final version to be published and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We express our gratitude to our institutions for their invaluable support, both in terms of time and financial resources.

Funding

CONAHCYT 377883 Ciencia de Frontera 2019 and Direction of Research, Hospital Infantil de México Federico Gómez, Code: HIM/2021/072.

Conflict of Interest

The authors declare no conflict of interest. Figs. 1,2,3,4,5,6 were created using BioRender. The authors have no financial or personal relationship with BioRender, and the use of this tool does not imply any endorsement.

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