Review

Cytomegalovirus and Cancer: Revisiting Oncogenic Hypotheses and Therapeutic Perspectives

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Cytomegalovirus and Cancer: Revisiting Oncogenic Hypotheses and Therapeutic Perspectives

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Abstract

Human cytomegalovirus (HCMV) has emerged as a potential oncomodulatory agent implicated in several cancers, yet its precise role in oncogenesis remains debated. This review synthesizes five decades of research on the involvement of CMV in cancer, focusing on molecular mechanisms by which CMV may promote tumor progression, including immune evasion, inflammation, and modulation of cell cycle pathways. We discuss evidence of CMV presence in tumors such as glioblastoma, breast, colorectal, and prostate cancers, and critically evaluate controversies surrounding its causal role. The review further explores current and emerging antiviral and immunotherapeutic strategies targeting CMV in oncological contexts, highlighting challenges and future research priorities. By reassessing oncogenic hypotheses and therapeutic avenues, this article aims to provide a comprehensive perspective on CMV's role in cancer biology and its potential as a target for cancer treatment.

Keywords: cytomegalovirus; cancer; viral oncogenesis; glioblastoma; antiviral therapy; oncomodulation

Introduction

Cancer is a multifaceted disease characterized by the uncontrolled proliferation of cells and their capacity to invade neighboring tissues and metastasize to distant sites [1]. Despite decades of research, cancer remains a leading cause of mortality worldwide, underscoring the complexity of its etiology and pathogenesis. The causes of cancer are multifactorial, involving genetic mutations, environmental exposures such as tobacco and radiation, lifestyle factors, and biological agents [2]. Among biological contributors, infectious agents, particularly oncogenic viruses, have been increasingly recognized as significant drivers in the initiation and progression of various malignancies [3]. Viruses are estimated to contribute to approximately 15–20% of human cancers globally, exerting their effects through diverse mechanisms including direct oncogene expression and chronic inflammation [4].

Human cytomegalovirus (HCMV), a member of the Herpesviridae family, infects a majority of the human population worldwide and establishes lifelong latency after primary infection [5]. Traditionally, CMV has been studied in the context of congenital infections and opportunistic disease in immunocompromised patients. However, emerging evidence over the past five decades suggests

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CMV's potential role in oncogenesis or as an oncomodulatory agent in various cancers. CMV DNA, RNA, and proteins have been detected in multiple tumor types, suggesting a possible contributory role in cancer biology [6–8]. This review aims to synthesize current knowledge on CMV's relationship with cancer, revisit oncogenic hypotheses, explore therapeutic implications, and highlight future research directions.

Biological Causes of Cancer: Viral Oncogenesis

The discovery that viruses can cause cancer revolutionized our understanding of oncogenesis. Several viruses have been firmly established as carcinogens, including human papillomavirus (HPV), Epstein-Barr virus (EBV), hepatitis B and C viruses (HBV, HCV), and human T-cell lymphotropic virus type 1 (HTLV-1) [9]. These viruses induce malignancy by integrating their genetic material into host cells, producing oncogenic proteins, and modulating cellular pathways that govern proliferation, apoptosis, and immune evasion [10].

For example, HPV induces cervical and other anogenital cancers through the E6 and E7 proteins, which inactivate tumor suppressor proteins p53 and retinoblastoma (Rb), leading to uncontrolled cell division [11]. EBV's latent membrane proteins promote B-cell transformation and contribute to lymphomas and nasopharyngeal carcinoma [12]. Chronic HBV and HCV infections induce liver inflammation and cirrhosis, creating a microenvironment conducive to hepatocellular carcinoma [13]. HTLV-1 encodes Tax, a transactivator that disrupts cell cycle checkpoints, promoting adult T-cell leukemia [14].

Beyond direct oncogene expression, chronic viral infections can cause persistent inflammation, DNA damage, and immune dysregulation, all contributing to a pro-carcinogenic environment [15]. Viral latency and reactivation can further contribute to genomic instability. Understanding viral oncogenesis has not only deepened insights into cancer biology but has also paved the way for virus-targeted therapies and vaccines.

Human Cytomegalovirus (HCMV): Virology and Pathobiology

Human cytomegalovirus is a double-stranded DNA virus classified in the beta-herpesvirus subfamily, characterized by its ability to establish lifelong latency after primary infection [16]. CMV infects a broad range of cell types, including epithelial cells, endothelial cells, fibroblasts, smooth muscle cells, and myeloid progenitors [17]. Primary infection is usually asymptomatic in immunocompetent individuals but can be severe in immunocompromised patients and neonates [18].

CMV establishes latency mainly in myeloid progenitor cells in the bone marrow and can reactivate under conditions of immunosuppression, stress, or inflammation [19]. Its genome encodes more than 200 proteins, many of which modulate host immune responses by downregulating major histocompatibility complex (MHC) molecules, interfering with cytokine signaling, and evading natural killer cell detection [20]. This immune evasion is critical for viral persistence and may also facilitate tumor immune escape mechanisms.

The global seroprevalence of CMV infection varies widely, ranging from 40% to nearly 100% depending on geographic region and socioeconomic factors [21]. Given its high prevalence and lifelong persistence, CMV infection represents a significant factor to consider in the etiology of diseases beyond classical viral syndromes.

Evidence Linking CMV to Cancer

The potential involvement of CMV in cancer was first suggested by the detection of CMV nucleic acids and proteins in various tumor tissues [22]. CMV presence has been reported in several cancer types, with varying degrees of detection and clinical significance (Table 1). Glioblastoma multiforme (GBM), a highly aggressive brain tumor, has been extensively studied with consistent detection of CMV DNA and proteins in tumor cells but rarely in adjacent normal tissue [23]. Other solid tumors

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such as breast cancer, colorectal cancer, prostate cancer, and medulloblastoma have also demonstrated CMV components within tumor cells, raising the hypothesis that CMV infection may influence tumor biology [24–27].

Table 1. Summary of Cancer Types with CMV Detection and Clinical Relevance.

Cancer Type	Detection Methods	CMV Prevalence*	Evidence of Oncogenic Role	Clinical Implications	References
Glioblastoma	PCR, IHC, in situ hybridization	High	CMV proteins detected in tumor tissue; promotes angiogenesis, immune evasion	Potential target for antiviral/immunotherapy	6,22,23,32,41
Medulloblastoma	PCR, IHC	Moderate	CMV antigens detected; possible role in tumor progression	Therapeutic target under investigation	25
Breast Cancer	PCR, IHC	Low to Moderate	CMV DNA and proteins found; correlation with tumor grade debated	Potential prognostic marker	27
Colorectal Cancer	PCR, IHC	Moderate	CMV presence linked to inflammation and tumor microenvironment modulation	Possible therapeutic implications	26
Prostate Cancer	PCR, IHC	Low	Limited data; CMV DNA occasionally detected	Role unclear, needs further study	[reference]

* Prevalence estimates vary by study and detection method.

Studies have shown that CMV gene products are expressed in tumor cells, suggesting active viral gene expression rather than latent infection or contamination [28]. Importantly, the localization of CMV in malignant but not normal tissues argues for a role beyond a passive bystander. Experimental infection of cultured cells with CMV has been shown to induce phenotypic changes relevant to cancer, including enhanced proliferation, increased invasiveness, resistance to apoptosis, and promotion of angiogenesis [29].

Nonetheless, the question remains whether CMV plays a causative role in tumorigenesis or acts as an oncomodulator that facilitates cancer progression and immune evasion.

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Molecular Mechanisms of CMV-Induced Oncogenesis

CMV encodes several proteins implicated in oncogenic processes. Immediate early (IE) proteins of CMV can manipulate host cell transcriptional programs, driving dysregulated cell cycle progression and survival [30]. The viral chemokine receptor homolog US28 has been shown to activate signaling pathways such as NF-κB and PI3K/Akt, promoting angiogenesis and cellular migration—hallmarks of cancer progression [31].

Moreover, CMV infection can inhibit apoptosis by upregulating anti-apoptotic proteins like Bcl-2 and modulating tumor suppressors, allowing infected cells to evade programmed cell death [32]. The virus induces pro-inflammatory cytokines and growth factors, remodeling the tumor microenvironment to favor cancer growth [33].

CMV-mediated downregulation of MHC class I molecules and interference with antigen presentation impairs cytotoxic T lymphocyte recognition, providing a mechanism for immune evasion within the tumor milieu [34]. Collectively, these mechanisms suggest that CMV acts as an oncomodulatory virus, facilitating tumor progression by altering host cellular pathways and immune surveillance.

Controversies and Challenges

Despite accumulating evidence, the role of CMV in cancer remains controversial. Some investigators argue that CMV detected in tumors reflects opportunistic infection of immunosuppressed cancer patients rather than a causative agent [35]. Differences in detection methods, sample handling, and population heterogeneity have led to variability in findings across studies [36].

Technical challenges in reliably detecting CMV in tumor tissues, including sensitivity and specificity of assays, contribute to these inconsistencies [37]. Moreover, it remains difficult to definitively establish causality in the presence of high CMV seroprevalence and frequent latent infection in the general population.

Addressing these challenges requires standardized, rigorous methodologies and longitudinal studies designed to dissect temporal and causal relationships between CMV infection and cancer development.

Current Status of Antiviral and Immunotherapeutic Strategies

Therapeutic strategies targeting CMV have been primarily developed for prevention and treatment of CMV disease in immunocompromised hosts, with antiviral agents such as ganciclovir, valganciclovir, and foscarnet being the mainstay of therapy [38]. However, the potential to repurpose these antivirals in CMV-associated cancers is an area of growing interest.

Preliminary clinical studies have explored the use of ganciclovir as an adjunct in glioblastoma treatment, reporting some improvement in patient survival [39]. Immunotherapeutic approaches targeting CMV antigens expressed in tumor cells are also under investigation, including CMV-specific vaccines and adoptive transfer of CMV-specific T cells [40]. These approaches aim to harness the immune system to specifically target CMV-infected tumor cells, potentially improving treatment efficacy and outcomes.

Novel strategies including small molecule inhibitors targeting CMV proteins involved in oncogenic pathways and immune checkpoint modulation are promising avenues for future cancer therapies. Various antiviral and immunotherapeutic strategies have been explored targeting CMV in oncological settings, as summarized in Table 2.

Table 2. Antiviral and Immunotherapeutic Strategies Targeting CMV in Cancer.

Therapy Type	Mechanism	Target Cancer Type	Key Findings	Status	References

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Valganciclovir	CMV DNA polymerase inhibitor	Glioblastoma	Improved survival reported in small trials	Clinical trials ongoing	32,39,41
CMV Peptide Vaccines	Stimulate CMV-specific T-cell response	Glioblastoma	Phase I trials show immunogenicity and safety	Early clinical trials	42
Adoptive T-cell therapy	Infusion of CMV-specific cytotoxic T-cells	Glioblastoma	Potential to enhance anti-tumor immunity	Preclinical/early trials	40
Antiviral drugs (Ganciclovir, Foscarnet)	Inhibit CMV replication	Various	Limited data on effectiveness in solid tumors	Off-label/experimental	18,38

Future Directions and Research Needs

The association between CMV and cancer demands further rigorous investigation. Future research priorities include the development and standardization of highly sensitive and specific detection techniques for CMV in tumors, large-scale epidemiological studies to establish associations, and mechanistic studies to clarify causal relationships [41].

Clinical trials are needed to evaluate the efficacy of antiviral and immunotherapeutic agents targeting CMV in cancer patients [42]. A multidisciplinary approach integrating virology, oncology, immunology, and molecular biology is essential to unravel CMV's complex role in cancer.

Additionally, understanding the impact of CMV infection on the tumor microenvironment and immune landscape may reveal novel therapeutic targets and strategies, advancing personalized medicine in oncology.

Conclusion

Human cytomegalovirus represents a compelling candidate in the landscape of viral oncogenesis. Evidence supports its role as an oncomodulatory virus that may contribute to tumor progression through multiple molecular and immunological mechanisms. Although controversies persist regarding its causal role, the therapeutic implications of targeting CMV in cancer are promising. Continued research is critical to translate these insights into improved diagnostic, prognostic, and therapeutic tools against CMV-associated malignancies.

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