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The Oncogenicity of Human Cytomegalovirus

Prakash Vishnu and David M. Aboulafia

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1. Introduction

The potential role of Human cytomegalovirus (hCM) infection in promoting neoplasia is an active area of scientific research. [1] Although still controversial, there is a growing body of evidence that links hCMV infection to a variety of malignancies, including those of the breast, prostate, colon, lung and brain (gliomas). [2-7] hCMV induces alterations in regulatory proteins and non-coding RNA that are associated with a malignant phenotype. These changes promote tumour survival by effecting cellular proliferation, invasion, immune evasion, and production of angiogenic factors [8] Constant immune surveillance governs the destruction of the majority of cancer cells and precancerous conditions in the human body. However, the most pathogenic of malignant tumors acquire immune evasion strategies which render them less vulnerable to destruction by immune cells.

The characteristic hallmarks of a malignant cell include:

1. sustaining proliferative signaling and evading growth suppressors,

2. resisting cell death and enabling replicative immortality,

3. inducing angiogenesis, activating invasion and metastasis. [9]

In cancers which are not attributable to infectious agents, chronic inflammation may also play a critical role in the transition from a precancerous condition to invasive malignancy. Inflammation is the seventh hallmark of neoplasia (Table 1). [10] During chronic inflammation, certain "promoters," such as hepatitis C virus and Epstein-Barr virus (EBV), may facilitate the transformation of a pre-malignant condition to neoplasia. [11,12] Cancer "promoters" are agents that, by themselves, may not have a significant oncogenic impact on normal cells but can drive precancerous cells towards neoplasia.

1. Sustaining proliferative signaling
2. Evading growth suppressors
3. Resisting cell death
4. Inducing angiogenesis
5. Activating invasion and metastasis
6. Enabling replicative immortality
7. Tumor-promoting inflammation

Table 1. The "seven" hallmarks of cancer

2. Chronic inflammation and oncogenesis

Associations linking chronic infection, chronic inflammation and malignancy have been well chronicled. [13] As many as 25% of all cancers can be traced to chronic infection or other types of chronic inflammation. [14] Infectious agents that cause chronic inflammation promote oncogenesis by complex pathways, and are depicted in Figure 1. Key mediators of inflammation-induced oncogenesis include generation of mutagenic chemical mediators such as reactive oxygen and nitrogen species, genetic variations in inflammatory cytokines [15], and creation of a micro-environment with features of chronic inflammation such as nuclear factor kappa B (NF-κB). [16,17] In such conditions, tumor-associated macrophages (TAMs) play a pivotal role in mediating inflammatory (M1) responses, as well as immunosuppressive and growth (M2) responses. [18]

M2-polarized TAMs and the related myeloid-derived suppressor cells are key components of smoldering inflammation that drives neoplastic progression. The M2 responses, while important for wound healing, can promote neoplastic transformation. TAMs respond to cytokines such as Interleukin (IL)-10 and Transforming Growth Factor (TGF)-β, acquiring M2 properties that promote immune suppression by blocking dendritic cell (DC) maturation and attracting regulatory T-cells (T-regs). [19,20] T-regs are potent inhibitors of the T-cell anti-tumor response. [21]

Activation of NF-κB pathway mediated by COX-2 and IL-6 via STAT-3 transcriptional activation also promotes malignant transformation. [22] NF-κB is a transcription factor that mediates an inflammatory cascade leading to generation of COX-2, an inducible isoform of nitric oxide synthase (iNOS) and the inflammatory cytokines IL-1β, IL-6, and Tumor Necrosis Factor (TNF) -α. These cytokines, in conjunction with nitric oxide produced by TAMs and tumor cells, are present in high concentration in the tumor microenvironment and are important promoters of inflammation-driven oncogenesis and immunosuppression. [23-25]
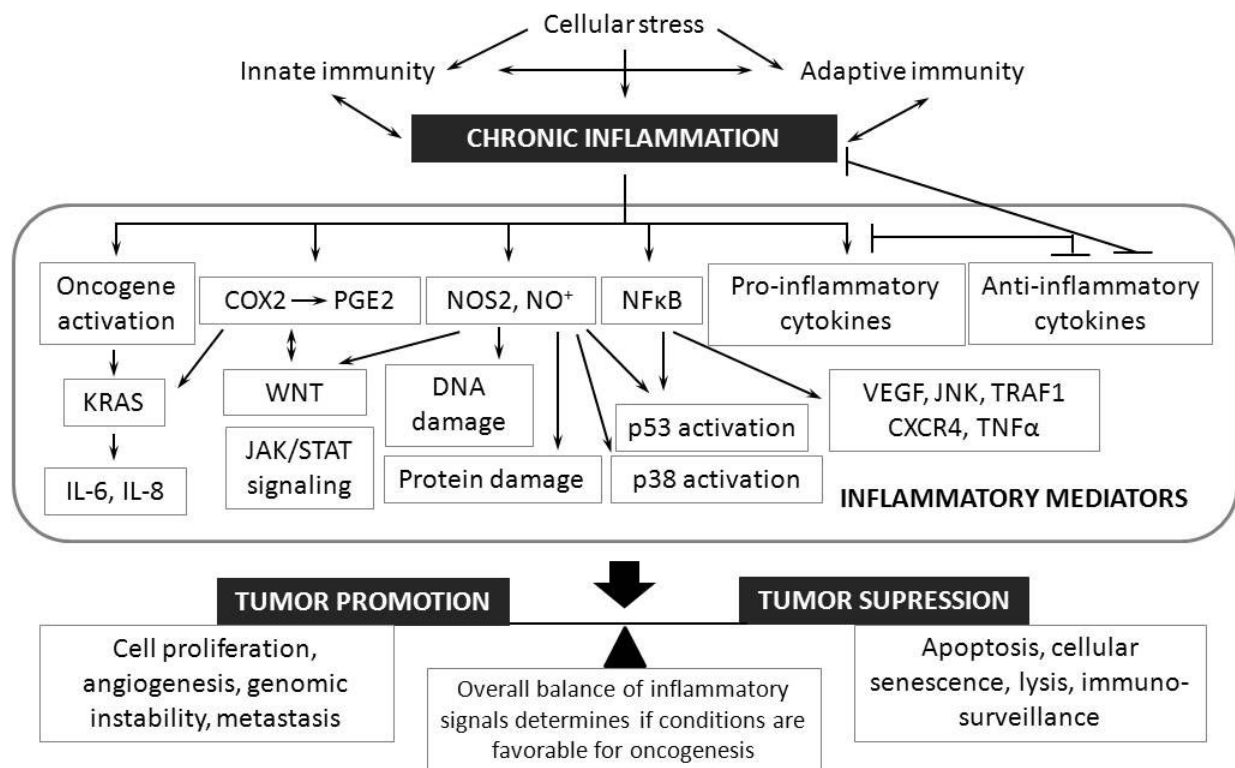
Figure 1. Pathway linking chronic inflammation and oncogenesis. (Adapted from Schetter et. al.[13])

3. Concept of oncomodulation

Tumor cells have aberrations in cell cycle signaling, RNA transcription and the production of tumor-suppression proteins. The concept of "oncomodulation" suggests that a virus may modulate cellular pathways [26] through changes to viral regulatory proteins and noncoding RNA which eludes to tumor cell properties (cell proliferation, survival, invasion, production of angiogenic factors, and immune evasion). hCMV not only promotes oncogenesis but also contributes to a more malignant tumor cell phenotype (Figure 2). While investigators have long postulated a role for hCMV in human neoplasia, many of the early studies were not reproducible and lacked clear *in situ* histopathological correlations with the proposed diseases. [27,28] The concept of "hit-and-run" oncogenesis holds that infection with hCMV takes place during an earlier time frame to tumour development. hCMV infection sets into motion processes resulting in malignancy, but the virus is no longer detectable by the time cancer occurs. [29] Several of the more important cellular pathways that could lead to cancer and which are modulated by hCMV are reviewed below.

3.1. Resistance to apoptosis

Resistance to apoptosis is a common feature of cancer cells. [9,30,31] Early research on hCMV infection revealed that hCMV protects the fibroblasts it infects from apoptosis. hCMV immediate early (IE) proteins (e.g., IE2-86 & IE2-72) [32] are able to prevent adenovirus E1A
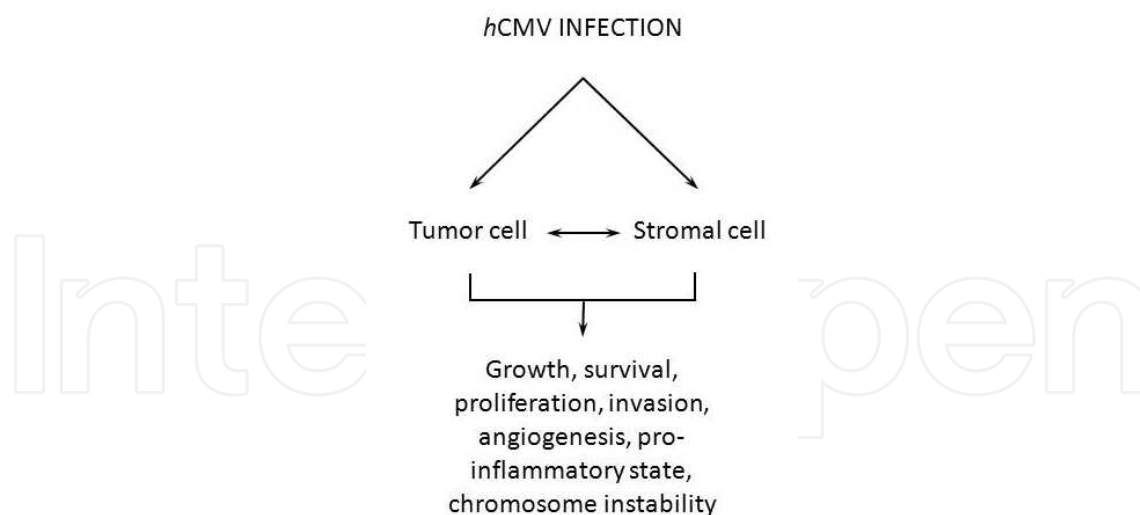
hCMV INFECTION

Tumor cell ⟷ Stromal cell

Growth, survival, proliferation, invasion, angiogenesis, pro-inflammatory state, chromosome instability

Figure 2. Concept of Oncomodulation. (Adapted from Michaelis et. al. [99])

protein-induced apoptosis-by both p53-dependent and independent mechanisms- of hCMV infected fibroblasts. Direct anti-apoptotic activity of hCMV proteins is related to defined transcripts encoded by the hCMV UL36-UL37 genes. [33,34] The product of the UL36 gene is an inhibitor of caspase activation which binds to the pro-domain of caspase-8 and inhibits Fas-mediated apoptosis. [35] Similarly, the UL37 gene product, UL37 exon 1, is a mitochondrial inhibitor of apoptosis and inhibits the recruitment of the pro-apoptotic proteins Bax and *Bak* to mitochondria, resulting in their functional inactivation. [36] hCMV further protects tumor cells from apoptosis by the induction of cellular proteins, including *AKT, Bcl-2, and ΔNp73α*. [37] Induction of the anti-apoptotic protein *Bcl-2* by hCMV, results in acquired resistance to cytotoxic drugs such as cisplatin and etoposide. This resistance can be reversed after treatment with the anti-hCMV drug, ganciclovir. [37] Engagement of platelet derived growth factor receptor (PDGFR) *α* or virus co-receptors (including integrins and Toll-like receptor-2) by hCMV glycoproteins can also lead to activation of mitogen-activated protein kinase (MAPK) and/or phosphatidyl-inositol 3-kinase (PI3-K) pathways that can alter apoptotic responses (Figure 3). [38-40]

3.2. Cancer cell adhesion, migration and invasion

Adhesion of cancer cells to endothelium is critical in promoting metastases. [41-43] hCMV can facilitate this process by promoting activation of integrins (e.g., β1α5 and B1) on the tumor cell surface, and by increasing adhesion of tumor cells to the neighboring endothelium. Tumor cell adhesion to endothelium is also facilitated by activation of integrin-linked kinases (e.g., phosphorylation of focal adhesion kinase Tyr397). [4,44] Down regulation of adhesion molecule receptors by hCMV (e.g., neural cell adhesion molecule, CD56), causes a focal disruption of endothelial cells facilitating tumor cell transmigration. [1,45] The net effects of hCMV on adhesion molecules account for decreased binding of cancer cells to each other and
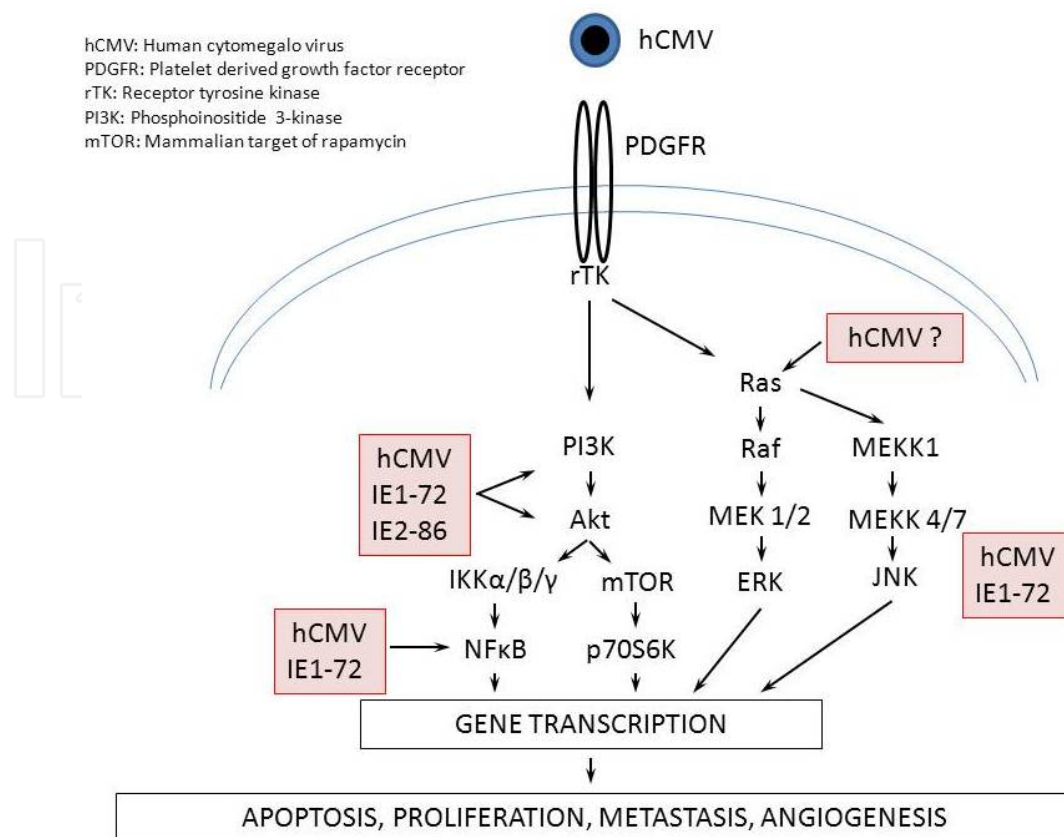
Figure 3. Major signaling pathways activated by hCMV that contribute to oncomodulation by hCMV. (Adapted from from Michaelis et. al. [100])

increased binding to endothelium, which is an important early process in formation of metastasis.

3.3. Angiogenesis

Angiogenesis is the growth of the new blood vessels and is essential for growth of malignant tumors. [9,46] Through the technique of secretome analysis researchers have shown that proteins secreted from hCMV-infected cells contain increased levels of pro-angiogenic molecules, and increased pro-angiogenic activity in cell-free supernatants. [47] US28 is a hCMV protein seen in high concentrations in the supernatant. This particular protein alters adhesion properties of epithelial cells inducing a pro-angiogenic and transformed phenotype through up-regulation of vascular endothelial growth factor (VEGF). [48] Additional supernatant proteins, including IE1-72 and IE2-86, increase vascular smooth muscle cell migration, proliferation, and expression of PDGF-β receptor. Furthermore, IE2-86 promotes endothelial proliferation by binding and inactivating the tumor oncogene p53 in endothelial cells. [49,50] Expression of IL-8, another well-recognized promoter of tumor angiogenesis, is increased by hCMV via transactivation of IL-8 promoter through the cellular transcription factors NF-κB and AP-1. [51] Binding of hCMV to and signaling through integrin β1, integrin β3, and epidermal growth factor receptor can also promote angiogenesis. [47,52]

Expression of thrombospondin (TSP-1), a potent inhibitor of angiogenesis, is suppressed in several hCMV-infected cancer cell lines, suggesting yet another mechanism by which hCMV can promote increased angiogenesis and a more malignant phenotype. [53,54] hCMV - mediated activation of COX-2 may also promote angiogenesis in tumor cells by inducing expression of Fibroblast Growth Factor (FGF), VEGF, PDGF, iNOS, and TGF-α, and by promoting capillary endothelial cell migration and tube formation (Figure 3). [55]

3.4. Impact of hCMV on cell cycle

In hCMV-infected host cells, viral regulatory proteins induce cell cycle arrest and prevent cellular DNA replication, whilst replication of viral DNA remains enabled. [8,56] While some hCMV regulatory proteins can induce cell cycle arrest, others can promote cell cycle progression. [57,58] hCMV IE2-86 induces cell cycle arrest by activating ataxia telangiectasia mutated (ATM) gene-dependent phosphorylation of p53, leading to p53- and p21-dependent inhibition of cell cycle progression. [59] In contrast, the hCMV regulatory proteins IE1-72, IE2-86, and the tegument proteins *pp*71 and UL97 interact with and deactivate proteins of the Rb family, promoting entry into S-phase of the cell cycle. [60]

The cell cycle of neoplastic cells is inherently dysfunctional. [9,31] In precancerous or transformed cells, the function of virus regulatory proteins may depend on the replicative status of the cell. [61,62] The hCMV protein US28 promotes cell cycle progression and cyclin D1 expression in cells with a neoplastic phenotype; whereas, it induces apoptosis in non-neoplastic cells. [48] Persistent hCMV infection of tumor cells may lead to a selection of virus variants with changes in virus regulatory proteins that have lost their ability to induce cell cycle arrest. [63,64]

4. Escape of immune surveillance by cancer cells: Role of hCMV

Immunological tolerance is a process by which the immune system no longer recognizes an aberrant antigen as "foreign." [67] Through "natural" or "self-tolerance" the body does not mount an immune response to self-antigens. "Induced tolerance" to external antigens can be created by manipulating the immune system. Mechanisms of tolerance that exist to prevent autoimmune disease may also preclude the development of an adequate antitumor response. [65-67] This concept of "immune tolerance" may be particularly important in malignancies whose etiology is associated with inflammation. [68] Expression of hCMV proteins by infected tumor cells may induce 'immune tolerance' to tumor cells. Also, several tumor-derived factors contribute to the emergence of complex local and regional immunosuppressive networks, including VEGF, IL-10, TGF-β, and prostaglandin E-2 (PGE2). [66,69]

hCMV has evolved multiple strategies for immune evasion resulting in persistent viral infection in the host [70-74] Several hCMV proteins, including those expressed with IE genes, block the host cell MHC class I antigen expression, which is essential for activation of CD8+ T-lymphocyte anti-tumor cytotoxicity. hCMV UL83 protein (pp65) blocks antigen presentation of hCMV epitopes to CD8+ T-cells, and expression of hCMV UL18, a MHC class I homologue,

disrupts "natural killer" (NK) cell recognition of hCMV-infected cells. [75] Disruption of hCMV antigen presentation by infected cells is mediated by hCMV protein US3, which sequesters MHC class I complexes in the endoplasmic reticulum, and hCMV protein US11 which causes dislocation of the MHC class I heavy chain from the cytoplasm. [76-78] hCMV-encoded IL-10 homologue impairs tumor antigen presentation by inhibiting maturation, normal differentiation and cytokine production of dendritic cells and macrophages.. [79-81] hCMV induces integrin $\alpha_v\beta_6$ expression in endothelial cells of blood vessels in different tissues, causing activation of TGF-β1, resulting in interference of host immune responses against tumor cells by blocking the activation of lymphocytes and monocyte derived phagocytes. [82] These direct immune-modulatory effects of hCMV on myeloid cells within the tumor microenvironment, along with expression of immunosuppressive cytokines provide a virtually impassable environment for the host anti-tumor immune system.

5. Influence of CMV on tumor microenvironment

Persistent hCMV infection of non-neoplastic cells in the tumor microenvironment leads to a paracrine secretion of inflammatory molecules that promote malignancy. [83] The secretome of hCMV-infected fibroblasts contains exceedingly high levels of growth factors, matrix remodeling proteins such as matrix metalloproteinases (MMPs), and angiogenic factors that signal through the TGF-β pathway. [47,84] These paracrine-secreted factors are also able to activate latent growth factors. PDGFs acts as strong mitogens and their overexpression is important in the pathogenesis of multiple malignancies. [85-87] In addition to growth factors, high levels of many ECM modifiers such as MMPs, tissue inhibitors of metalloproteinases (TIMPs) and urokinase receptor (uPAR) secreted by hCMV infected cells aiding, tumor invasion and metastasis. [84]

6. DNA mutations, impaired DNA repair mechanisms and epigenetic changes by hCMV that leads to genomic instability

hCMV infection can drive neoplastic transformation by causing chromosome damage and genetic instability in infected cells, particularly in vulnerable adult stem cells. [88-90] hCMV in combination with cytotoxic chemotherapy agents synergistically increases genotoxic effects. [91,92] The virus can induce specific chromosome 1 strand breaks at positions 1q42 and 1q21 in a replication-independent fashion, both of which are associated with DNA repair and replication genes. [89,93,94] hCMV IE1-72 and IE2-86 proteins when in conjunction with other viral oncogenic proteins (e.g., adenovirus E1A protein) that disrupt cell cycle can induce oncogenic transformation. [29]

hCMV can contribute to genomic instability through a variety of different pathways. In brief, the virus may induce chromosomal aberrations (e.g., production of micronuclei, misaligned chromosomes, chromosomal lagging and bridging) by hCMV UL76 protein. [95,96] The virus

can also disrupt DNA repair pathways, including the activity of ATM and ATM-Rad3 (ATR). [97] More recently, hCMV has been shown to modulate oncogenesis through the telomerase pathway by activating human telomerase reverse transcriptase (hTERT) in fibroblasts and malignant cells. [98]

7. Conclusions

Significant advances have been made in understanding the roles of chronic inflammation, tumor microenvironment, cancer stem cells, tumor immunology, and infectious agents in the pathobiology of cancer. Several clinical and experimental findings suggest that hCMV may play a role in promoting certain cancers. In cells that are persistently infected with hCMV, the expression of viral proteins may prevent the immune system from identifying or removing these cells, thereby offsetting immune detection of transformed cells. The effects of hCMV in promoting tumor cell immune evasion may prove important in development of cancer immunotherapies, particularly if the hCMV-infected cells are resistant to the action of cytolytic peptides released by activated NK and cytotoxic T-cells. Also, if viral proteins that inhibit apoptosis are expressed by hCMV infected tumour cells, the cancer cells may be less suscep- tible conventional chemotherapeutic agents. Whether hCMV is ultimately established as an oncogenic virus will require additional research in the areas of virology, epidemiology and molecular oncology, and systematic refinement of the concept of "oncomodulation." Insights into the role of hCMV in oncogenesis may increase understanding of cancer biology and promote development of novel therapeutic strategies.

Author details

Prakash Vishnu[1] and David M. Aboulafia[1,2*]

*Address all correspondence to: david.aboulafia@vmmc.org

1 Floyd & Delores Jones Cancer Institute at Virginia Mason Medical Center, Seattle, WA, USA

2 Division of Hematology, University of Washington, Seattle, WA, USA

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