Accelerated cancer aggressiveness by viral oncomodulation: New targets and newer natural treatments for cancer control and treatment

Russell L. Blaylock
Theoretical Neuroscience Research, LLC, Ridgeland, MS, United States.
E-mail: +Russell L. Blaylock - blay6307@gmail.com

ABSTRACT
An infectious etiology for a number of cancers has been entertained for over 100 years and modern studies have confirmed that a number of viruses are linked to cancer induction. While a large number of viruses have been demonstrated in a number of types of cancers, most such findings have been dismissed in the past as opportunistic infections, especially with persistent viruses with high rates of infectivity of the world’s populations. More recent studies have clearly shown that while not definitely causing these cancers, these viruses appear capable of affecting the biology of these tumors in such a way as to make them more aggressive and more resistant to conventional treatments. The term oncomodulatory viruses has been used to describe this phenomenon. A number of recent studies have shown a growing number of ways these oncomodulatory viruses can alter the pathology of these tumors by affecting cell-signaling, cell metabolism, apoptosis mechanisms, cell-cell communication, inflammation, antitumor immunity suppression, and angiogenesis. We are also learning that much of the behavior of tumors depends on cancer stem cells and stromal cells within the tumor microenvironment, which participate in extensive, dynamic crosstalk known to affect tumor behavior. Cancer stem cells have been found to be particularly susceptible to infection by human cytomegalovirus. In a number of studies, it has been shown that while only a select number of cells are actually infected with the virus, numerous viral proteins are released into cancer and stromal cells in the microenvironment and these viral proteins are known to affect tumor behavior and aggressiveness.

Keywords: Cytomegalovirus, Microenvironment, Oncomodulation, Viral proteins

INTRODUCTION
The cell and carcinogenic transformation
The cells in a multicellular organism possess a massive number of systems to ensure not only the survival of individual cells but also the organism as a whole [Figure 1]. This requires a very complex number of cellular mechanisms at several levels, from the cellular membrane enclosing the cell to the various compartments and membranes within the cell. Hundreds of complex cell-signaling operations occur constantly within the cell in a series of process that entail nuclear DNA instructions as well as membrane information transfer to the cytosol. Various cell signals utilize a number of similar cell-signaling pathways in a finely tuned and highly coordinated way.
The metabolism of the cell entails a coordinated system of nutrient breakdowns, biosynthesis of essential molecules, and selection of metabolites to be utilized on an ongoing basis.

Cells also need protection from the toxic substances in its environment and need to maintain their physical structure, metabolic functions, and other maintenance requirements as the microenvironment changes. During development, and even adult maintenance, a progenitor cell may adapt to become a skin cell, a neuron, or a bone cell or an inflammatory cell from its library of contained cell instructions.

The nucleus of the cell contains its inherited library of genetic information in its DNA template. This information is stored in the DNA in its coding and noncoding sections and in the histones around which the DNA is wrapped. Specialized proteins are constructed in the nucleus on membranes in the large nuclear organelle, the nucleolus. These proteins are constructed as directed by the information contained in the nuclear library. The biochemical reactions needed for the cell to survive are selected from information in a molecular form that comes from the cellular microenvironment. All of these processes require energy sources derived from molecular reactions primarily located in mitochondrial DNA and supplied by nutrients or even in extreme circumstances from its own molecules to survive and to function. The nuclear membrane has channels to communicate with the cytosol. That is the nuclear membrane specifically allows the transport of selected molecules in and of the nucleus, especially the mRNA or message templates from the nuclear DNA that direct the cell's various functions in the cytoplasm as well as receiving instructional transcription molecules from sites within the cytosol. The DNA itself is dynamically influenced by epigenetic signals (developmental factors in utero and during childhood, environmental chemicals, drugs, pharmaceuticals, aging, diet, and other environmental influences.) that can rapidly alter the instructions being given the cell [Figure 2].

The cytoplasm, or cytosol, contains water, amino acids, and organelles for the construction of proteins, which come from information derived from the nucleus. These proteins are made on short templates that come from the nucleus as mRNA protein molecules and attach to cytoplasmic membranes on the ribosomes located on the Golgi apparatus. In the cytosol, glucose, and other energy molecules are broken down or catabolized to supply energy to operate these and other metabolic processes.

The mitochondria, which contain their own genetic information, provide a major source of energy from metabolites, like pyruvate, which is formed during the process of glycolysis in the cytoplasm. Pyruvate and other metabolites enter the mitochondrion and are broken down and enter the mitochondrial tricarboxylic acid (TCA) cycle.
to produce high yields of energy molecules such as adenosine triphosphate (ATP). These energy molecules drive all the energy-demanding biochemical reactions, many membrane transporters, and other such functions taking place in the cell. Much of the cell’s protection is energy dependent.

Cell-signaling pathways consist of a complex series of interacting molecules within the cytoplasm and are activated by molecules from various extracellular and membrane receptors stimulated and influenced by both extracellular and intracellular signals. These extracellular activating molecules drive the cell to respond by affecting cell signaling pathways and influencing metabolism. Some signaling pathways are designed to trigger cell death (apoptosis) and others can stimulate the cells to survive, grow, and proliferate. It has been generally held that mutations in the nuclear DNA drive the cell to become a cancer cell. However, this long-held concept is now being challenged. As a result, a major change in our thinking about the origins and treatment of cancer is occurring.

Compelling evidence from multiple lines of the study suggests that most cancers are either the result of chronic inflammation or made more aggressive and deadlier as a result of prolonged and/or intense inflammation. The process of cancer induction can include general inflammation within the body (extrinsic inflammation) or localized inflammation (intrinsic) within the tumor microenvironment. Likewise, a growing number of carcinogenic factors are found to be inflammatory, such as chronic irritation, chemical carcinogens, bacterial, fungal, and viral infections, parasitic infections, and exposure to ionizing radiation. What all these have in common is the induction of inflammation.

Is cancer a genetic and/or a metabolic disorder?

Mechanisms linking inflammation with all stages of cancer development have been elucidated in a number of recent studies. The search for a common cause for cancers in general has, until recently, been focused on activation of cellular DNA oncogenes with subsequent overactivation of specific cell-signaling pathways. Seyfried et al. have recently shaken the oncology world by suggesting, supported by a great deal of evidence, the idea that cancer is not a genetic disorder, but rather a metabolic disease.

Among his many studies, Seyfried has shown that cells, on malignant transformation, rapidly undergo radical changes in metabolism that favor both (a) an elevation in energy supplies and how this energy is generated and (b) rerouting of metabolism for biosynthesis of macromolecules needed for cell reproduction. To accomplish these changes requires major metabolic shifts commandeering cystolic and mitochondrial processes linked to metabolism, principally by switching metabolism to (i) favor glycolysis that takes place not only in the cytoplasm but also in the mitochondria and a (ii) redirecting the TCA cycle in the mitochondria for biosynthesis of macromolecules, production of nucleotides, and supplying substrates for membrane lipids and TCA cycle intermediates, in addition to making the general fuel source of metabolism, molecular ATP [Figure 3].
The cancer process is also dependent on suppressing apoptosis (programmed cell death), inhibiting tumor suppressor mechanisms (p53, p21, and PTEN), and stimulating cell growth factors (Bcl-2, platelet-derived growth factors [PDGFs], basic fibroblastic growth factor, etc.) from the mitochondria [Figure 1]. Once the cancer transformation takes place, a number of mechanisms are activated to ensure cancer cell survival. For example, the cancer cells as well as surrounding stromal cells in the microenvironment generate special immune-suppressing proteins and release immune-suppressing exosomes, thus altering immune competence (especially anticancer immune surveillance), while promoting angiogenesis and inflammation within the tumor microenvironment. In most human cancers, we eventually see massive mutation of genes, rather than activation of one or a few critical oncogenes. Most of these cancer cell oncogenes have to do with inflammation, immune function, angiogenesis, tumor suppression mechanisms, and various aspects of essential cancer cell-signaling. In most human cancers, we eventually see massive mutation of genes, rather than activation of one or a few critical oncogenes. Most of these cancer cell oncogenes have to do with inflammation, immune function, angiogenesis, tumor suppression mechanisms, and various aspects of essential cancer cell-signaling.

One of the unanswered questions is - How would a cancer cell, by random mutations, know which oncogenes were essential for its survival, eventual invasion of surrounding tissues, massive proliferation of cells, activation of a complex process, and finely tuned processes, such as the angiogenesis programs, and, in an exactly determined way, create metabolic alterations favorable to its growth and spread? Random mutations caused from damage by reactive oxygen and nitrogen species, one would think, would activate genes that were not only favorable to tumor growth but also equally be unfavorable, being that reactive oxygen and nitrogen genetic injury would be rather haphazard.

The actual conversion of a precancer cell into a fully cancerous cell appears to involve a series of steps that must be rather exacting so as to turn on cell survival mechanisms and suppress programmed cell death mechanisms. This not only entails cell-signaling pathways but also alterations in metabolism, which appear to be quite dynamic as cancer progresses.

**VIRAL CAUSATION OF CANCER: THE EVIDENCE GROWS STRONGER**

There are some 1400 human pathogens that include 220 viruses. It is recognized that a variety of infectious agents can contribute to the carcinogenic process. Cancer cell transformation can occur either by (1) genetic insertion of viral oncogenes in the cell's genome or (2) by suppression of protective cell processes. This suppression can include blocking of anticancer immunity, activation of chronic inflammation, promotion of genetic instability, or

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Figure 3: Cancer Cell Metabolism involving its two major fuels, glucose and glutamine. Demonstrates role of c-MYC in induction of glutamine addiction. Myc consist of a family of regulator genes (proto-oncogenes) coding for transcription factors. The Myc family consists of c-myc, l-myc and n-myc. Also demonstrates the influence of growth factors on cancer cell-signaling.
suppression of apoptosis mechanisms, each or all of which can promote transformation of the cell into a cancer cell. There is growing evidence that overactivation or increased presence of cancer-related cell-signaling pathways alone can transform some cells into cancer cells, especially cancer stem cells.[76,103]

Of greatest concern regarding cancer are those viruses that show persistence following acute infection. The most common persistent human pathogens include the herpes group of viruses, which include herpes simplex 1 and 2, cytomegalovirus, Epstein-Barr virus (EBV), herpesvirus-6, and herpesvirus-7. In the past, researchers referred to viruses linked to cancer causation as being oncogenic viruses. These viruses become oncogenic by a number of mechanisms, including induction of chronic inflammation, insertion of specific viral genes into the cell’s genome, inducing overexpression of carcinogenic cell signaling pathways, and altering cell metabolism.[126]

Until rather recently, viruses were classified as being capable of oncogenic transformation by the fact that they inserted their oncogenic genetic structure into the cells’ genome.[27,128] A newer classification of cancer-related viruses has been introduced referred to as oncomodulating viruses, in which, rather than actually initiating cancer, the virus plays a major role in the pathological behavior of the previously transformed cells.[45]

What is oncomodulation?

Oncomodulation involves the production of a number of protein viral products in the cell’s cytoplasm that promote tumor cell invasion, proliferation, angiogenesis, immune suppression, altered expression of cell-signaling pathways, inhibition of apoptotic mechanisms, and suppression of tumor inhibitors, such as PTEN, pRB, p53, and p21.[47] Intensive examination of the cancer process has disclosed a great deal of information concerning cancer cell metabolism and the exact mechanisms operating tumor cell proliferation, migration, tumor cell invasion, and immune suppression, as well as cell signaling pathways involved in these processes.

Armed with this information, it becomes obvious that all of these processes are fine-tuned to promote survival of the cancer cells against the cell’s and body’s defense mechanisms. One must ask how could cancer cells know exactly what cell mechanisms and cell signaling pathways would be needed to accomplish these goals and how to fine-tune them. The likelihood of this occurring by a totally random process of DNA damage initiated by a storm of reactive oxygen and nitrogen products, as stated, seems illogical. Yet, viruses are programmed to carry out a very similar series of processes within infected cells to ensure not only viral reproduction but also prolonged survival in a latent state.

The real debate is now between the idea that cancerous cells are merely favorable niches for these viruses or whether these viruses can actually induce cancer and then control its behavior. Compelling evidence suggests that oncomodulatory viruses can control the behavior of transformed cells and some evidence strongly suggests that certain viral proteins can induce cancerous transformation.[165,126] That is, persistent viruses, even in the latent stage, make cancers more aggressive by causing them to proliferate faster, become more invasive, and metastasize sooner, and more extensively - that is, these infected cancer cells become deadly, as well as resistant to conventional treatments, such as radiation and chemotherapy.

Rather than discuss a number of persistent viruses linked to oncomodulation, I will focus on two of the most likely candidates, mostly human cytomegalovirus (HCMV) and less so herpes simplex virus type 1 (HSV-1). Other oncomodulatory viruses include SV-40, human adenovirus and human papillomavirus type 16 and 18.[47] The main trigger for activation of oncomodulatory viruses appears to be inflammation, especially chronic inflammation.

Viral mechanisms in cancer cell development

Making a link between viral infections and cancer transformation of normal cells demands some rather strict criteria as well as methodology and technology that was not available until relatively recently. In 2002, Cobbs et al. reported the presence of HCMV protein and nucleic acids in virtually all glioblastomas (GBM) they examined but not in normal brain tissue.[49] Others were not able to reproduce these results.[109,151,170] In 2011, a symposium was held in Washington, D.C. to study the issue and reach a consensus utilizing the expertise of oncologists and virologists.[47] The difficulty between the supporters of the hypothesis (linking viruses and cancer) and its detractors, the group concluded, was found to be a lack of uniform operational definition of viral positivity within tumor tissue and the use of techniques of insufficient sensitivity in the negative studies. In other words, in the negative studies, there were no agreed-on definitions of viruses affecting cancer cell behavior and the techniques of viral detection, and both criteria were found to be inadequate at the time. They also concluded that HCMV was definitely involved in significant tumor oncomodulation and possible tumor initiation, the latter requiring more evidence. It has now been established that 90%–100% of GBM, medulloblastomas, prostate adenocarcinomas, breast cancers, colon cancers, and mucopidermoid cancers of the salivary glands contain HCMV nucleic acids and viral proteins.[11,84,167,184,196,205]

Viruses (HCMV) can induce altered metabolism in stem cells

It was assumed in earlier studies, and some later studies, that for the virus to play a role, it must infect most of the tumor
cells. Ranganathan et al. found in their frozen specimen studies of GBM that most of the tumor cells were not infected with the virus, rather only a select number of cells were actually infected, with other cells containing viral proteins known to affect tumor behavior. The authors suggested that the virus may be preferentially infecting cancer stem cells. This has been confirmed by Odelberg et al., who found that HCMV preferentially infects stem cells. Hence, unlike other recognized oncogenic viruses, where all tumor cells are infected, in the case of HCMV, one sees viral proteins as the inducers of tumor aggressiveness and invasiveness, since actual insertion of the viral genome is not necessary for oncomodulation [Figure 4 and Table 1].

**Mutated HCMV causing induction of cells to become tumors**

Some have suggested that it is mutated HCMV viruses that are responsible for these findings of enhanced tumor aggressiveness. Dolan et al., for example, found that mutant forms of HCMV grew slowly in tissues, a requirement for oncomodulation. These mutated forms of HCMV, which characteristically grow slowly and yield fewer virions than wild type viruses, have been found in osteosarcomas, glioblastoma, and neuroblastomas. It has also been shown that latent HCMV viruses can affect tumor cell behavior, yet more likely the greatest effect is by mutated viruses that reproduce slowly and in low numbers and may explain why viral-induced carcinogenesis only affects a small percentage of HCMV-infected individuals. In essence, it has been demonstrated that persistent viral infections are essential for oncomodulation.

The latent virus may be inactive only in so far as viral reproduction and not production of the oncomodulatory proteins. Important is the observation that the mutated viruses are not fully latent, rather produce viral offspring at a very slow rate, while still generating hundreds of viral proteins that can alter tumor cell behavior.

**Chronic inflammation and HCMV infection**

Chronic inflammation is now considered not only a major trigger for oncogenic transformation but also drives cancer at all stages of development. There exists a paradoxical increase in inflammation in the tumor microenvironment and a concomitant decrease in antitumor immunity. Inflammatory mediators are critical to cancer initiation, progression, proliferation, angiogenesis, invasion, and...
metastasis and involve a number of cell-signaling pathways and transcription mediators, such as STAT3, NFκB, chemokines, cytokines, proinflammatory prostaglandins (PGE2), and other inflammatory mediators [Figure 3]. The tumor microenvironment consists of over 50% nontumor stromal cells, which include an assortment of immune cells (tumor-associated macrophages [TAMs], dendritic cells, tumor-associated neutrophils, NK and NKT cells, B lymphocytes, and T-lymphocytes), cancer fibroblast, adipocytes, vascular endothelial cells, pericytes, and lymphatic endothelial cells. These cells, along with the cancer cells themselves, are the sources of these inflammatory and immune suppressing factors. This crosstalk between tumor stromal cells and cancer cells control tumor behavior.

Cytokine interleukin (IL)-6 and activation of HCMV

Inflammation is also known to activate HCMV, and the proinflammatory cytokine IL-6 (from monocyte and macrophages) appears to play a particularly important role in its activation from a latent stage. The effects of IL-6 on HCMV behavior are especially important, not only in that it activates latent HCMV viruses but also because it has been shown to affect a limited subset of genes and proteins that are critical for oncomodulation. IL-6 also upregulates bone marrow X-linked (BMX) and STAT3 proteins in both infected and uninfected cells. BMX kinase, is overexpressed in glioma stem cells (GSC) and plays a major role in tumor growth. STAT3 plays an important role in tumor proliferation, invasion, angiogenesis, and immune suppression, primarily through stimulation of inflammatory pathways such as NFκB and IL-6 [Figure 1].

High levels of IL-6 have been associated with a poor prognosis in several types of cancer [Figure 1]. The major source of IL-6 within the tumor microenvironment arises primarily from tumor cells and tumor-associated fibroblast. HCMV-infected endothelial cells also secrete cytokines and chemokines, such as IL-6, TNF-alpha, granulocyte-macrophage colony-stimulating factor (MCF), macrophage inflammatory protein-1, mononuclear protein-1, and other inflammatory mediators.

| Table 1: NCMV proteins and their oncogenic effects on cell mechanisms |
|-------------------------|-------------------------|-------------------------|-------------------------|
| **pUL83**               | **pUS2**                | **pUS28**               |
| **pUL16**               | **pUL122**              | **vIL-10**              |
| **pUL122**              | **pUL123**              | **pUL97**               |
| **pUL122**              | **pUL123**              | **pUL37X1**             |
| **pUL36**               |                         |                         |
| **pUL122**              |                         |                         |

**Immune Suppression**
- IL-6, Rantes, MCP-1 activation (enhanced inflammation)
- VEGF--Angiogenesis (invasion and metastasis)
- NFκB activation (enhanced inflammation)
- Deregulated cellular energetics (Warburg Effect)
- Prolonged STAT3 activation (pUL111A) [Immune suppression]

**Genomic instability**
- pUL123
- pUL83
- pUL82

**Inhibition of p53, Rb suicide genes**
- pUL122
- pUL123
- pUL97

**Inhibition of Apoptosis**
- (Cell proliferation and survival)
- pUL122
- pUL123
- pUL37X1
- pUL36

**Activation of PI3K/Akt**
- pUL122
metalloproteinases (MMPs). Another way HCMV enhances inflammation is by activation of NFkB, which increases the release of inflammatory cytokines such as TNF-alpha and IL-6 within the tumor microenvironment, both from tumor stromal cells and tumor cells. HCMV immediate early genes (IE) IE-1-72, IE-2, IE-2-86, and IE2-55 regulate NFkB activation. NFkB is dramatically activated in most cancers [Figure 5].

Chemotherapy, radiotherapy, and other carcinogens in the activation of HCMV through Inflammation

It has also been shown that chemotherapy and radiotherapy can activate HCMV, which could lead to more aggressive cancers following treatment failures. Interestingly, both of these conventional treatments dramatically increase inflammation, a known activator of HCMV. Other known carcinogens, such as industrial chemicals, pesticides, herbicides, and several plant-based carcinogens, also induce inflammation and therefore are candidates for HCMV activation. The delay in carcinogenic conversion of these exposed cells, even in the case of radiation, may be secondary to required metabolic and cell-signaling changes that would occur over a long period. Accumulated mitochondrial energy deficits, required for the carcinogenic process, may also take time to develop.

Furthermore, of interest is the finding that the viral load of HCMV correlated with survival in glioblastoma patients. In

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**Figure 5:** Activation of COX-2 leading to generation of prostaglandins (PGE2) and subsequent enhancement of inflammation. Tumor cell proliferation, angiogenesis and suppression of anti-tumor immune activity are enhanced in the face of tumor microenvironment inflammation. The central role played by NFkB, found in all cells, is demonstrated. Activation of this factor occurs in the stromal cells, tumor cells and invading immune cells within the tumor microenvironment. PGE2 activation of JAK2/STAT3 acting on genes controlling tumor invasion/migration, cell proliferation, angiogenesis and initiating immune suppression is demonstrated.
one such study, those with low levels of the virus lived twice as long as those with the highest titers.\textsuperscript{17,149}

In one study, nearly 80% of glioblastoma patients were found to have HCMV DNA detected in their peripheral blood, which was assumed to be from shedding of the virus by the tumor.\textsuperscript{132}

Another interesting link to cancer behavior is the finding that NFκB differentially regulates the oncogene promoter c-Myc.\textsuperscript{108} Levels of c-Myc, as well as other protooncogenes, such as c-fos and c-jun, are rapidly upregulated following HCMV infection of cells.\textsuperscript{20,21}

The role of chronic inflammation, HCMV, and cancer cell induction

Within the brain, HCMV infection is associated with microglial activation and migration of activated macrophages to the infected brain.\textsuperscript{166} In a study of newborn infections in mice it was found that the HCMV virus preferentially invaded the external granular layer of the cerebellum and that the granule cell progenitor cell numbers were increased, thus thickening the external granular layer, a site of origin of medulloblastomas and primitive neuroectodermal tumors.\textsuperscript{173} Blocking TNF-alpha in these infected animals prevented the thickening of the external granular layer and reduced infiltration of mononuclear cells. It was determined that the principle source of the TNF-alpha was the activated microglia.\textsuperscript{188} HCMV can persistently infect glioma cells and are reactivated by inflammation within the tumor microenvironment and with immunosuppression.\textsuperscript{24,48}

CYTOMEGALOVIRUS (HCMV) TARGETS STEM CELLS

It has been hypothesized that mutations in preneoplastic cellular tumor suppressor proteins, such as PTEN, p53, and p21, and fluctuations in the cellular microRNA profile could explain why to develop malignancies, but the most important link is to HCMV-infected stem cells.\textsuperscript{102} Inflammation, and associated generation of reactive oxygen and nitrogen radicals, would be a major mechanism by which these proteins are mutated. Cytomegalovirus infections have a preference for progenitor cells (stem cells) in both congenital infections and in adult infection, as shown by its preference for localizing in the ventricular and subventricular zone where the densest concentration of stem cells reside.\textsuperscript{147}

HCMV virus has been shown to inhibit differentiation of stem cells into neurons but not astrocytes.\textsuperscript{107,142} Susceptibility to HCMV infection declines with differentiation into neurons, but HCMV can infect mature astrocytes.\textsuperscript{187} PDGF and its receptor are essential for stem cell self-renewal, and PDGF inhibits stem cell differentiation into neurons, astrocytes, and oligodendrocytes.\textsuperscript{189} The PDGF ligand is a powerful stimulus for transformation of progenitors into malignant gliomas as seen with retroviruses expressing PDGF [Figure 4].\textsuperscript{19} Interestingly, the HCMV virus is activated by PDGF alpha, which is absolutely required for HCMV virus entry into cells, activation of essential downstream signaling, and eventual viral replication.\textsuperscript{189} The importance of the cancer stem cells is emphasized by the finding that a single GSC can produce a glioma-like tumor in animal models.\textsuperscript{78}

Both BMX kinase and IL-6 drive and maintain GSCs.\textsuperscript{82,180} It has also been shown that HCMV infection upregulates stemness regulators in GSCs. For example, in an in vitro study, it was shown that at 5 weeks following infection, cellular markers for glioblastoma stemness, and aggressiveness signature (CD44, CEBPBβ, OLIGO2, and SOX2) were up-regulated as compared to controls.\textsuperscript{74} One of the hiding places for latent HCMV viruses is within-host adult stem cells such as hematopoietic stem cells in the bone marrow - a major site of HCMV persistence.\textsuperscript{182} It has also been shown that HCMV gene products are expressed at higher levels in CD133+ stem-like cells fractions, than other glioma cells, again indicating the preference of HCMV viruses for stem cells.\textsuperscript{124}

Because stem cells play such a key role in the generation of cancerous tumors, as well as their maintenance and migration, the finding that HCMV preferentially infects these cells and could activate virtually all of the essential cancer cell-signaling pathways and induce critical metabolic changes within cancer stem-like cells, explains why infections of all of the cells of a tumor is not necessary for oncomodulation.

Cytomegalovirus and tumor-induced immune evasion

One of the early events in tumor development is suppression of antitumor immunity.\textsuperscript{112} A number of immune cells can kill cancer cells, including natural killer cells, cytotoxic T-lymphocytes (T-cells), and macrophages (microglia in the brain). It has been shown that in each case, most of these cells can be shifted to do just the opposite - that is, block immune killing of cancer cells.\textsuperscript{14} Initially, these immune cells were described as either being in an M1 (killer mode) or M2 (immune suppression mode) phenotype, with the ability to switch back and forth as needed. It is now thought that rather than being two modes of immune function, these cells actually transition along a greater range of activity.\textsuperscript{93} For convenience sake, I will use the older classification - M1 and M2.

Tumor microenvironment and immune cells suppressing antitumor activity

It has been observed that the tumor microenvironment generates factors that suppress antitumor immunity early in the course of the carcinogenic transition. This involves not
only cancer cells but also surrounding stromal cells, which are induced by the tumor cells to release immune evading and suppressing mediators. These immune-suppressing mediators include PGE2, anti-inflammatory cytokines, chemokines, and COX-2. PGE2 interacts with noncancer cells in the tumor microenvironment, which stimulates inflammation but also suppresses antitumor immunity.\(^{[213]}\)

**Role of inflammation in the growth of tumors; COX-2 is a tumor growth factor and NSAIDs inhibit of COX-2**

It has been established that an inflammatory tumor microenvironment is crucial for sustained tumor cell proliferation, immune evasion, suppression of apoptosis mechanisms, angiogenesis, tumor invasion, and tumor cell migration. Tumor cell-induced COX-2 within the tumor microenvironment activates PGE2, which also promotes tumor growth by stimulating inflammation-driven stem cell signaling pathways essential for tumor behavior.\(^{[213]}\) COX-2 is known to be elevated significantly in a number of tumors and suppression of COX-2 by NSAIDs can significantly inhibit the development, as well as growth and invasion, of many of these tumors.\(^{[63,119,162]}\) NSAIDs also reduce virus-mediated PGE2 production and reduce the viral burden in HCMV infected cells.\(^{[193,209]}\) Celecoxib, the specific COX-2 inhibitor, has been shown to reduce PGE2, as well as HCMV expressed proteins in medulloblastomas along with reducing tumor growth both in vitro and in vivo.\(^{[12]}\)

Interestingly, combining antiviral drugs with COX-2 inhibitors significantly inhibited tumor growth in mice engrafted with human medulloblastoma tumors, more so than when the antiviral was used alone [Figure 3].\(^{[12]}\)

**HCMV generated proteins that are immune suppressant and tumor stimulating**

It has been shown that HCMV generates a number of special proteins in the tumor cell such as US28, which can bind different chemokines external to the tumor cell in its environment such as CCL2, CCL5, and CX3CL1 and thus suppressing antitumor immunity.\(^{[59,190,191]}\) Other HCMV viral proteins associated with immune suppression in the tumor microenvironment include US11, US2, US3, US8, which block cytotoxic T-cell killing, and US3 and US58 which block CD4+ T-cells. Cancer cells expressing the HCMV viral protein UL16 are protected against NK and cytotoxic T-cell destruction.\(^{[94]}\)

HCMV US28 viral proteins have also been shown to upregulate high levels of COX-2 in HCMV infected cells.\(^{[11]}\) HCMV is also known to establish latency in myeloid lineage cells and that reactivation of the virus is dependent on inflammation. By persistently infecting monocytes/macrophages, the virus can induce strong inflammatory responses when these cells are migrating to the tumor microenvironment.\(^{[186]}\) The infiltrating TAMs are switched to the M2 immunity-suppressing mode within the tumor microenvironment.

Studies have shown that HCMV protein expression has been detected in infiltrating inflammatory cells within the tumor microenvironment in human breast and colon cancers.\(^{[35,85]}\) Similar infiltrations of inflammatory macrophages and microglia cells by HCMV have been detected in gliomas.\(^{[192]}\) HCMV is known to stimulate the immune suppressing cytokines IL-10 and transforming growth factor-β (TGF-β) within infected tumors.\(^{[68]}\)

**Immune cells using IL10 cytokine and other factors to delay immune activation against the tumor; Also by HCMV**

One of the more prominent immune inhibitors generated by human immune cells is IL-10, a T-helper (Th)-2 cytokine. Some pathogens use IL-10 to delay immune activation so as to establish infection.\(^{[157]}\) HCMV encodes a UL11A gene product that is closely related functionally to human IL-10 (cmvIL-10), which has very potent immunosuppressive properties through inhibiting mononuclear proliferation, suppression of cytokine production, inhibition of dendritic cell maturation and migration, and downregulation of MHC expression.\(^{[155,195]}\) In glioma cells, cmvIL-10 is expressed early during stages of HCMV infection. As mentioned, GSCs are preferentially infected in vivo by HCMV as are macrophages and microglia within the glioblastoma cell microenvironment, which also produce cmvIL-10.\(^{[66]}\) Also, of importance, was the finding that cmvIL-10 treated monocytes produce angiogenic vascular endothelial growth factor (VEGF) and immunosuppressive TGF-β, which enhances tumor cell growth and migration. Overall, HCMV-infected monocytes/macrophages within the tumor microenvironment greatly increase the production of immunosuppressive factors such as VEGF, IL-10, TGF-β, and PGE2.\(^{[10]}\) The virus HHV-6 is known to upregulate immunosuppressive cytokine IL-10 and inhibit antitumor IFN-γ, thus engineering a shift from Th1 to Th2 phenotype immunity.\(^{[3]}\) Of interest is the finding that reactivation of HHV-6 is usually associated with reactivation of other herpesviruses such as HCMV and EBV.\(^{[130]}\)

Through a complex interaction between tumor cells and TAMs (immunosuppressive macrophages/microglia), HCMV infections appear to impair tumor antigen presentation by dendritic cells within the tumor microenvironment.\(^{[51]}\) HCMV UL83 gene product pp65, which is found consistently in glioblastoma cells, blocks antigen presentation of viral protein IE1.\(^{[51]}\)

It is evident that HCMV controls a number of tumor cell and stromal cell mechanisms within the tumor microenvironment that can prevent antitumor immunity from functioning.
HCMV-ACTIVATED SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION (STAT) PROTEINS AND IMMUNE EVASION

STATs stimulate inflammatory response and direct antiimmune environment around the tumor

STAT family of proteins, within immune cells and tumor cells within the microenvironment, consists of seven members, STAT 1-6 and closely related STAT5A and STAT5B, which control specific biological responses [Figures 1 and 4].[207] Of these proteins, STAT3 appears to play a major role in promoting immune evasion by the tumor, but it also controls tumor invasion, angiogenesis, and other tumor promoter mechanisms.[216] STAT3 has also been shown to regulate glioblastoma stemness.[82] The cytokine IL-6 upregulates BMX kinase and STAT3 proteins in both infected and uninfected cells. BMX knockdown (removal) has been shown to suppress tumor growth.[82,86] STAT3 selectively induces and maintains an inflammatory tumor microenvironment that supports cancer at all its stages.[81,216] In addition, STAT3 and less so STAT5 and STAT6 play a major role in inhibiting antitumor immunity.[106,131,169] By selectively inhibiting antitumor activities of NFκB and STAT1, STAT3 antagonizes Th1 cytokines such as IL-12 and interferon-γ, which are critical for innate T-cell antitumor immunity.[106,228] STAT3 is essential for expression of inflammatory cytokines such as IL-1β, IL-6, MCF, PGE2, and COX-2 necessary for maintaining the inflammatory tumor microenvironment.[229] Immune inhibitors, such as STAT3, can increase inflammation while at the same time reducing antitumor immunity.

Both NFκB and STAT3 are persistently activated in cancer cells, where they function as nuclear transcription factors required for activation of genes involved in tumor proliferation, survival, angiogenesis, immune evasion, and tumor invasion.[105,227] STAT3 is also involved in suppressing innate antitumor immunity by promoting the conversion of antitumor macrophages into immune-suppressing TAMs and by stimulating the migration of myeloid-derived suppressor cells (MDSCs) to the tumor microenvironment.[40,105] Both STAT3 and STAT6 have been implicated in stimulating immunosuppressive MDSCs.[106,125,145] In addition, STAT3 mediates expansion of immune suppressing regulatory T-cells (Tregs) within tumors [Figure 6].[105]

Crosstalk intercellular communication between tumor cells in the tumor microenvironment inhibiting antitumor immunity

The persistent activation of STAT3 within tumor cells crosstalks with surrounding immune cells within the tumor stroma and microenvironment to inhibit antitumor immunity.[203,228] It has also been shown that overexpression of IL-6-JAK-STAT pathway can drive carcinogenic behavior without gene mutation.[163]

Activation of STAT 3 signaling by other viruses and other agents

A number of tumor viruses can activate the STAT3 pathway, including HCMV, EBV, HPV, HTLV virus, and hepatitis B virus [Figure 6].[112,138,183,204] STAT3 can also be activated by other noninfectious stresses, including direct lipopolysaccharide stimulation through toll-like receptor 4 immune activation, UV light induction of skin cancer, chemical carcinogenesis, and chronic stress.[4,104,168] In the case of colitis-induced carcinoma, we see that STAT3 signaling is required for cancer induction.[22] In fact, in the absence of STAT3, in experimental carcinogen-induced colorectal cancers, one sees continued inflammation without tumor formation.[22]

Figure 6: Demonstrating persistent activation of STAT3 by inflammatory cytokines within the tumor environment, which activates cytoplasmic REL/NFκB chronically. In combination, this suppresses anti-tumor immunity and stimulates tumor cell proliferation.
How STATs influence gene regulation and apoptosis, leading to suppression of the immune response to tumors and to Stimulation of tumor cell growth and invasion mechanisms

Closely linked and critical to STAT3 pathway activation is the cytokine IL-6, downstream from NFκB, COX-2, which is also downstream from NFκB, is involved in cancer inflammation and activates STAT3 through IL-6 [Figure 6].

A number of inflammatory cytokines can activate STAT3 through NFκB/IL-6 signaling, including IL-17, IL-21, and IL-23.

NFκB has a dual role in cancer, acting either an anticancer pathway or procancer pathway by regulating different sets of genes. STAT3 inhibits the expression of the anticancer gene regulation by NFκB through inhibiting genes that normally would activate Th1 innate immunity and adaptive immunity used in controlling tumor growth.

The procarcinogenic factor RELA is persistently activated in tumor cells and tumor-associated immune cells and requires continuous activation of STAT3. REL, a regulator of immunostimulating cytokines and chemokines needed for antitumor immunity, is not activated in cancer cells. In addition, STAT3 can directly antagonize STAT1, which prevents one of the major antitumor pathways from operating.

By activating STAT3, HCMV viruses affect a number of cancer processes including proliferation, invasion, migration, angiogenesis, and inhibition of apoptosis. Virtually, all of the alterations we see regarding immune evasion by cancers can be initiated by HCMV infections.

HCMV INHIBITION OF APOPTOSIS MECHANISMS CONTROLLED WITHIN THE MITOCHONDRIA

Cancer cells universally inhibit apoptosis by a number of mechanisms. Virtually every mechanism used to inhibit apoptosis can also be utilized by HCMV viruses, to not only suppress apoptosis but also to inhibit other tumor cell survival mechanisms. For example, in myeloma cells, IL-6 drives JAK-STAT3 pathway activation, which upregulates antiapoptotic genes [Figures 1 and 5].

Most apoptosis mechanisms are controlled within the mitochondria, initiated through extrinsic activation of death signals acting on TNFR1, fas, or trail receptors, which then cleave precursors to release caspase 8 and 9 [Figure 7]. A large number of viral products (viral genome directed molecules) are localized in the mitochondria and interact with mitochondrial proteins to suppress metabolic systems and apoptosis mechanisms.

The viral gene locus UL37 produces one of the most abundant viral proteins in HCMV infections, pUL37x1/vMIA, which is one such inhibitor of apoptosis. This viral factor has potent antiapoptotic activity by binding to BAX apoptotic protein on the outer mitochondrial membrane (OMM). HHV-8 virus produces a glycoprotein, K7, which has structural homology to survivin, an antiapoptotic cellular protein, which inhibits BAX-induced apoptosis by tethering Bcl-2 and active caspase-3 to inhibit caspase apoptotic activity.

As pointed out by Williams and Colberg-Poley, viruses may encode death receptor decoys, regulate endogenous death receptor expression, direct caspase inhibitors, modulate Bcl-2 family of proteins, or express their own viral homologous cellular Bcl-2 protein family members, to evade apoptosis.

The antiapoptotic viral Bcl-2 homolog protein molecules are commonly employed by all gamma-herpesviruses, such as HCMV, as a mechanism of cellular persistence. Similar Bcl-2 protein homologous produced by these viruses include KsBcl-2 and K7 protein of HHV-8, E1B-19K of adenovirus, and BHRF1 and BALF-1 of EBV. E1B-19K protein also interacts with p53 to suppress mitochondrial-mediated apoptosis induced by p53.

Viruses encoded proteins can control cell suicide genes such as p53 and retinoblastoma proteins (Rb) [Figure 5].

The major antiapoptotic members include Bcl-2 and Bcl-XL. It has been shown that HCMV-infected neuroblastoma cells were significantly less sensitive to cytotoxic anticancer drugs, such as cisplatin and etoposide, than noninfected cells. Treating the infected cells with the antiviral drug ganciclovir-restored cytotoxic sensitivity to the drugs.

Other mechanisms responsible for evading cell death, such as enhancement of telomerase and a shift in error-prone DNA repair, are also playing a role in viral evasion of tumor cell apoptosis. It has been shown that HCMV induces constitutive activation of human telomerase reverse transcriptase (hTERT) in malignant glioma cells lines and most malignancies. It is activation of hTERT that shifts the balance toward DNA repair. Straat et al. demonstrated that ectopic expression of the HCMV protein IE72 alone, of over 200 viral proteins, was sufficient to reproduce the viral effect on hTERT promoter activation and increased production of telomerase in cancer cells. It has also been shown that constitutional activation of hTERT is sufficient to immortalize normal diploid cells.

Viral gene IE1 was also found to inactivate p53 and Rb tumor suppressors, while at the same time upregulating the activity of the procancer cell signaling pathway PI3-K/AKT, which enhances tumor cell survival. IE1 viral genome expression in malignant gliomas is positively correlated with the grade of the tumor with GBM having the highest levels. This viral gene factor is also correlated with survival in glioblastoma patients. HCMV IE1 gene is found in most tumors and causes proliferation of glioblastoma cells.
Activation of the PI3K/Akt cell signaling pathway is also important for inhibition of apoptosis in tumor cells, primarily by inhibiting the apoptosis factor BAD and restoring the antiapoptotic factors bcl-XL and bcl-2. Many factors can activate PI3K/Akt pathway and several viruses, including some herpes viruses, such as EBV and HCMV viruses, have been shown to activate this tumor essential signaling pathway. Akt activation has been correlated with the depth of tumor cell invasion, infiltration of venous blood vessels, lymph node metastasis, and stage of the disease.

**TUMOR ANGIOGENESIS INDUCED BY VIRAL PROTEINS**

Angiogenesis begins very early in tumor growth. This new blood vessel growth is needed to bring nutrients and oxygen to the tumor microenvironment. There are a number of known proangiogenic proteins released into the tumor microenvironment from tumor cells, such as VEGF, basic fibroblast growth factor (FGF), FGF-binding protein (BP), CXC chemokines (CXCL8, CXCL1), placenta-like growth factor, TGF-β, platelet-derived endothelial growth factor (PD-EGF), and pleiotrophin. Fibroblasts, near the tumor bed, also produce proangiogenic factors. The tumors themselves recruit progenitor endothelial cells from the bone marrow, used to construct new blood vessels. In addition, angiogenic suppressor proteins used to inhibit angiogenesis released by stromal cells in the tumor microenvironment, such as thrombospondin 1 and 2, are inhibited. The hypoxic tumor microenvironment triggers the release of hypoxia-inducible factor (HIF)-1α from tumor cells, which upregulates several of these angiogenic factors. HIF-1 is a transcriptional factor whose release is triggered by hypoxia and plays a critical role in the cell's response to reduced oxygen tension, including angiogenesis. Tumor-induced angiogenesis involves both arterial and lymphatic endothelial proliferation. In addition, HIF-2α has been shown to convert stem cells to cancer stem cells and induced breast cancer chemotherapy resistance by activating Wnt and Notch pathway cell signaling. Wnt and Notch signaling play a key role in the development of cancer stem cells and stemness maintenance. Tumor hypoxia is associated with...
a high-grade malignancy, a poor prognosis and is associated with resistance to chemotherapy and radiotherapy.

Viral oncoproteins from several types of viruses have also been shown to stimulate the production of several angiogenic factors, including VEGF and FGF-BP, by stimulating their gene promoters in the nucleus.\textsuperscript{[116,199]} HCMV infections have been shown to impair the expression of the angiogenic suppressors TSP-1 and TSP-2 in several cell lines, including glioblastoma cell lines.\textsuperscript{[43]} Loss of these suppressor proteins enhances angiogenic vessel growth. It has been shown that a lack of TSP-2 gene expression was significantly associated with a higher histological tumor grade as well as density of angiogenic vessels in glioblastoma tumors in patients, and TSP-1 expression is inversely correlated with tumor vascularity in colon cancer metastasis.\textsuperscript{[100,120]}

HCMV infections are characterized by a widespread presence of viruses in the vessel walls of major arteries throughout the body.\textsuperscript{[87]} CMV is known to infect and insert viral proteins in all cell types involved in angiogenesis, including endothelial cells, smooth muscle cells, pericytes, fibroblast, and macrophages.\textsuperscript{[28]} It has been shown that HCMV is unique among herpes viruses in promoting the release of a number of soluble factors (secretome) involved in angiogenesis.\textsuperscript{[86]} The viral secretomes also contain a number of factors, such as MMPs that penetrate vessel walls and tissue basal membranes. In essence, the HCMV secretome proteins play a major role in all aspects of angiogenesis and thus modulates the cancer process in established tumors.

**METABOLIC ONCOMODULATION**

**Change from oxidative phosphorylation to aerobic glycolysis in tumor cell metabolism (Warburg effect) and the role of HCMV**

Cancer cell metabolism plays a critical role in cancer cell behavior. These metabolic pathways offer a valuable target for treating and possibly curing many of the more aggressive cancers. One of the characteristics of cancer cells is a radical shift in metabolism that occurs quite early in the carcinogenic process.\textsuperscript{[173]}

In the 1920s, Otto Warburg hypothesized that mitochondrial dysfunction was the cause of most cancers and that cancer cells switched from oxidative phosphorylation to aerobic glycolysis during malignant transformation of cells.\textsuperscript{[217]} Recent studies have confirmed Warburg’s hypothesis, yet the process is not always operational since in conditions of need, cancer cells can temporally switch back to oxidative phosphorylation.\textsuperscript{[72]} Porporato et al. have pointed out that malignant cells show considerable metabolic plasticity, being able to shift metabolism as conditions in the tumor microenvironment change during tumor progression.\textsuperscript{[132]}

One of the early events in malignant cell transformation is the dramatic increase in glucose uptake. This is accomplished in malignant cells by an increase in glucose transporters, GLUT1, and GLUT3, with higher levels of activation being associated with a poor prognosis.\textsuperscript{[6,73]}

Rapidly proliferating cells have a need for accelerated macromolecule biosynthesis, such as amino acids, nucleotides, and lipids. This need is met by reducing mitochondrial respiration, which allows accumulation of intermediate precursors from glycolysis, which are then used for such synthesis, mainly through the pentose phosphate pathway [Figure 8].\textsuperscript{[133]} In addition, by reducing mitochondrial energy production by the Krebs cycle and the electron transport system, fewer free radicals are produced that could trigger apoptosis. Other mitochondrial apoptosis systems are also inhibited by the metabolic switching of metabolism, as well as inhibition of mitochondrial antitumor immunity.

Interestingly, HCMV has been shown to also reprogram infected cells toward a Warburg-like metabolism [Figure 8].\textsuperscript{[136]} Moreover, as we saw in the case of cancer cells, a great deal of glycolysis is directed toward macromolecule synthesis.\textsuperscript{[136,137]} This glycolysis switch increases the production of substrates for the biosynthesis of nucleotides, fatty acids, and lipid for viral reproduction.\textsuperscript{[10,197]}

HCMV-infected cells also require an increased supply of glucose. By switching GLUT1 to GLUT4, the virus allows glucose to be transported at a rate threefold higher than can be attained by GLUT1.\textsuperscript{[230]} This increases the rate of aerobic glycolysis.

The efflux of glucose carbons from TCA cycle forms citrate, which supports fatty acid synthesis in a similar way to tumor cells.\textsuperscript{[136,137]} It is important to appreciate that HCMV viruses upregulate metabolic and biosynthetic enzymes needed for increasing the activity of glycolysis, which both increases ATP generation as well as macromolecule biosynthesis.\textsuperscript{[136]} Removal of citrate from the citric acid cycle in HCMV-infected cells has the same effect in as in tumor cells, that is, a great decrease in glucose-derived carbon in the TCA cycle, which decreases the biosynthetic intermediates and ATP.\textsuperscript{[137]}

**Glutaminolysis as a source of energy production**

In Figures 3, 8, and 9, as glycolysis only produces two ATP molecules, both cancer cells and the HCMV-infected cells require glutamine for most of its energy production.\textsuperscript{[34]} Glutamine uptake is increased during HCMV infection, as in tumor cells, by the process of glutaminolysis. Inside the cell, glutamine interacts with the enzyme glutaminase producing glutamate, which is then converted into alpha-ketoglutarate by the enzyme glutamate dehydrogenase, which then enters
Krebs cycle, thus supplying metabolic intermediates for the Krebs pathway (anaplerosis) taking place in the mitochondria [Figure 8].\textsuperscript{[60,222]} This is similar to what we see in tumor cell metabolism.\textsuperscript{[140]} Glutamine starvation in cultures using most normal cells has little impact, but in the case of cancer cells overexpressing c-Myc, glutamine deprivation induces death due to glutamine dependence.\textsuperscript{[137,231]} c-Myc triggers a transcriptional program that promotes glutamine uptake and conversion to alpha-ketoglutarate, resulting in glutamine addiction.\textsuperscript{[222]} Several studies have shown that c-Myc mRNA and protein levels are elevated in HCMV infections.\textsuperscript{[20,135]} The glutamine starvation effect can be reversed using pyruvate or oxaloacetic acid.

Glutamine stimulates a further accumulation of lactate (through malate formation), which increases glycolysis and NADPH generation, and this buffers oxidative stress within the cells, thus protecting the virus and the tumor cell.\textsuperscript{[60]} Glioblastoma cells develop high rates of glutamine metabolism, which is the preferred source of carbon for biosynthesis of metabolic intermediates.\textsuperscript{[60]} Inhibiting glutamate dehydrogenase, the rate-limiting enzyme for alpha-ketoglutarate generation, has been shown to be an effective anticancer strategy for GBM when combined with agents that deplete glucose and inhibit specific kinases, such as Akt.\textsuperscript{[225]} Catechin gallate and epigallocatechin-3-gallate, from green tea have been shown to inhibit glutamate dehydrogenase, which converts glutamate into alpha-ketoglutarate to be utilized for substrate formation.\textsuperscript{[114]}

It is assumed by many researchers that the beneficial effect of glutamine metabolism for the tumor cells rests on supplying TCA cycle intermediates for biosynthesis of metabolic products, generation of glutathione and generation of NADPH required to keep glutathione in a reduced state.\textsuperscript{[222]} Yet, considerable evidence suggests that glutamate accumulates outside the cancer cell, and changes in tumor behavior are directly related to glutamate interacting with...
glutamate receptors, both on tumor cells and stromal cells within the tumor microenvironment.

**Glutamate, glutamate receptors, and tumor behavior**

Circulating levels of glutamate are elevated in breast and prostate cancer patients (as well as a number of other tumor types) and high levels signify a poor prognosis. In a recent study of breast cancers, serum levels of glutamate, but not glutamine or lactate, were elevated in tumor-bearing animals over time. In the study, using a primary mammary carcinoma model, researchers measured a broad range of metabolites in the circulation and found that only glutamate levels correlated with tumor burden, with the tumors themselves being the source of the glutamate [Figure 3]. The tumor released glutamate at a rate that correlated with glutamine consumption. They did not see glutamate accumulating around normal breast epithelial cells, even with glutamine consumption. Inhibition of the system Xc-antiporter using sulfasalazine, potently reduced the glutamate release by the tumors. System Xc-antiporter is a cellular mechanism that exchanges extracellular cystine for intracellular glutamate, which raises extracellular glutamate levels. Normally, this extracellular glutamate is removed by the glutamate transport proteins, such as GLT-1 (EAAT-2). What this study demonstrates is that elevated levels of extracellular glutamate are derived not primarily from glutaminolysis but rather the system Xc-antiporter. Excess glutamine, in this case, is converted within the cell by glutaminase to glutamate and is then converted into alpha-ketoglutarate to be used as a substrate for the cancer cell.

Further, they demonstrated that glucose depletion had no effect on invasiveness, but depletion of glutamine significantly reduced invadopodia protrusions and length. Adding glutamate to the medium restored invasive protrusions. That glutamate receptors on the invadopodia were involved in tumor invasion was demonstrated by the finding that inhibiting Group II metabotropic glutamate receptors also inhibited invasive protrusions on tumor cells. Antagonizing Groups I and II metabotropic glutamate receptors had no effect on invasiveness. Using a metabotropic glutamate receptor Group II agonist (LY40) promoted invasiveness.

Transmembrane release of matrix metalloproteinase (MMP) plays a major role in proteolytic invasion of the surrounding matrix by cancer cells. In cancer cells, MMPs becomes concentrated within the invadopodial structure. Another study confirmed that glutamate plays a major role in activating the MMP system. Normal breast epithelial cells secrete very little glutamate as compared to cancer cells. In this same study, exposing normal breast epithelial cells to high levels of glutamate led to increased recruitment of matrix MMP vesicles to the plasma membrane and resulted in invasion of the basement membrane surrounding the extracellular matrix. They concluded that glutamate increased tumor invasion by stimulating Group II metabotropic GRM3 glutamate receptors, which enhanced trafficking of MMPs to the cell surface of the invadopodia, thus increasing tumor invasion.

Tumor cells are not the only source of high levels of glutamate, as stromal fibroblast within the tumor microenvironment can also release very high levels of glutamate. Extracellular and plasma glutamate levels have been shown to be predictive of survival in medulloblastomas. For example, Wilson et al. found that glutamate levels were significantly predictive of survival among 35 cases of medulloblastoma despite other known risk factors. Glutamate levels were predictive of survival in high-risk patients alone, with patients with low glutamate levels being alive 8 years after diagnosis and patients with high levels dying within 1 year. Patients with c-Myc overexpression had the worst prognosis and the highest glutamate levels, as they are more dependent on glutamine than glucose. It is known that medulloblastomas with overactivation of c-Myc have the poorest prognosis. This process applies to other tumors as well.

**Glutamate receptors and tumor invasiveness**

Ye et al. demonstrated that high-grade pediatric gliomas released high levels of glutamate that enhanced tumor invasiveness by a process of excitotoxicity at the leading edge of the tumor. Others have shown that stimulating calcium-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (GluR2-lacking AMPA receptors) also stimulates tumor cell proliferation, invasion, and mobility. Even though gliomas contain no functional N-Methyl-D-aspartic acid (NMDA) receptors (having low levels of the NRI subunit), inhibiting of these receptors inhibits proliferation and migration of glioma cells.

How the NMDA receptor antagonists are inhibiting tumor proliferation and migration is not specifically known but it may be through inhibiting ERK1/2 and CREB phosphorylation, cell signaling pathways that regulate cell proliferation, differentiation, and tumor survival in neural tumors, which include medulloblastomas and high-grade gliomas. Ectopic expression of glutamatergic mGluR1 in normal melanocytes has been shown to cause hyperproliferation and transformation to malignant tumors.

**Failure of glutamate clearance from the tumor microenvironment**

Interestingly, it has been found that glioma cell lines isolated from patient’s malignant gliomas lack the glutamate transport protein EAAT-2 (GLT-1), which is the main glutamate clearing protein in the brain. This is especially important in that GLT-1 is critical for clearing extraneuronal glutamate
resulting from overactivity of system Xc-antiporter. When this happens, glutamate levels can rise significantly in the brain's extraneuronal space, driving tumor proliferation, invasion, and metastasis (migration). In monolayers of glioma cell cultures, cystine, the substance exchanged for glutamate, can raise extraneuronal glutamate levels some 500-fold within a few hours.\(^{[188,226]}\)

**Calcium and tumor growth**

It is known that calcium oscillations play a critical role in tumor invasion and tumor cell migration (metastasis).\(^{[121]}\) NMDA receptors are essentially nonfunctional in gliomas as the leading cellular calcium transport receptor. Calcium oscillations (waves of variations in calcium concentration) in the tumor microenvironment arise from calcium permeable AMPA receptors, which lack the GluR2 subunit [Figure 10].\(^{[61,188]}\) Glutamate receptors are constructed of a number of subunits, and the GluR2 subunit is essential for inhibiting calcium permeability to the AMPA receptor. [Tables 2 and 3] Ishiuchi et al. and others demonstrated the essential role played by these special glutamate receptors by transfecting the GluR2 subunit into glioma cells (making the calcium impermeable), which made them unable to respond to glutamate with calcium oscillations.\(^{[91,188]}\) When these altered tumors were implanted into animals, the tumors were unable to invade. Ishiuchi et al., as well as others, also demonstrated that glioblastoma cells highly expressed GluR1 and GluR4 subunits, which increased the tumor's invasive properties.\(^{[90,148]}\) Calcium-permeable AMPA receptors were seen to be more numerous in medulloblastomas and ependymomas as well.\(^{[25]}\) Activation of calcium-permeable AMPA receptors has been shown to inhibit human glioblastoma apoptosis by activation of Akt, the cell survival signaling pathway that also promotes tumor cell migration.\(^{[42,91,133]}\) Likewise, inhibiting AMPA receptors inhibited activation of the anti-apoptotic Akt pathway.\(^{[91]}\) The Akt cell signaling system is central to tumor behavior and survival.\(^{[62,179,187]}\)

One of the important links to viral infections and other inflammatory conditions to the aggressive behavior of cancer is that inflammation increases trafficking of GluR2-lacking AMPA receptors (calcium permeable AMPA receptors) [Figure 10].\(^{[19,146,221]}\) Considerable evidence suggests that these special AMPA receptors increase intraneuronal calcium levels and trigger calcium oscillations that activate tumor cell invasion and motility.\(^{[118]}\) Glioma released glutamate has also been shown to stimulate the growth of malignant gliomas.\(^{[206]}\)

**VACCINATIONS USED TODAY AND THEIR POTENTIAL THREAT IN THE CAUSATION OF CANCER**

Of great interest is the finding that even a single viral protein, such as US28, when injected in an experimental animal can result in tumor development.\(^{[126]}\) This is of real concern in
No real effort is being made to remove these viral fragments and proteins from vaccines. With millions of people being vaccinated with these contaminated vaccines, a real and present danger of disease induction exists, including induction of cancers. Even with nononcogenic viruses, the oncomodulatory effects would have the potential to make many cancers much more aggressive and therefore deadly.

Little comfort comes from claims of no evidence of human disease from these vaccine contaminants, as most studies are not long term. If we use HCMV as a prototype, with a large percentage of people in the world carrying the virus, while it is not associated with causing cancer, as this paper shows, it has major oncomodulatory effects on established cancers.

**NEUTRACEUTICALS AND THEIR ANTIVIRAL EFFECT AS A TUMOR SUPPRESSOR**

It has been shown that several naturally occurring compounds, such as curcumin, quercetin, baicalin, luteolin,
and resveratrol can suppress replication of a number of viruses both in vitro and in vivo.\textsuperscript{[58,70,71,117,139,210,223]} Curcumin has also been shown to be a powerful inhibitor of IL-6, which plays a critical role in all cancers and HCMV oncomodulation.\textsuperscript{[79]} In addition, these compounds have been shown to not only have anticancer effectiveness when used alone but also enhance the effectiveness and safety of traditional treatments, such as radiotherapy and chemotherapy.\textsuperscript{[186,202,208,215]} Several natural compounds also inhibit immunoexcitotoxicity and can lower glutamate levels.\textsuperscript{[18,194]}

Grape seed proanthocyanadins extract has been shown to reduce calcium entry associated with calcium-permeable AMPA receptors, which during states of inflammation constitute a major source of intracellular calcium and calcium oscillations.\textsuperscript{[1]}

**CONCLUSION**

The new finding that certain viruses, while not definitely transforming normal cells into tumor cells, can have dramatic effects on their behavior at all levels of the carcinogenic process. By an oncomodulatory series of mechanisms, viruses can make several cancers more aggressive and more likely to metastasize. The HCMV produces over 200 proteins, only a few of which have to do with viral replication - most being involved in altering host cell behavior.\textsuperscript{[186]}

Unfortunately, despite the clear demonstration of oncomodulation by this virus and others, viral testing is not routine for cancer patients. Of even more concern, is the fact that utilizing antiviral treatments along with traditional treatments is not routine, but in my opinion, should be. A number of cited studies have shown that such combinations can significantly improve long-term survival, even for some of the more aggressive cancers, such as glioblastoma, inflammatory breast cancer, and medulloblastoma.

It appears reasonable, based on the literature, to test all cancer patients for the presence of HCMV, EBV, and HSV-1 and 2, and if found to be infected, these patients should undergo antiviral treatments - either natural or pharmaceutical.

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