ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.surgicalneurologyint.com

Surgical Neurology International
Editor-in-Chief: Nancy E. Epstein, MD, NYU Winthrop Hospital, Mineola, NY, USA.
SNI: Neuro-Oncology
Editor
Mitsutoshi Nakada, MD
Kanazawa University, Ishikawa, Japan

SNI
Open Access

Review Article

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

***Corresponding author:**
Russell L. Blaylock,
Theoretical Neuroscience Research, LLC, Ridgeland, MS 39157, United States.

blay6307@gmail.com

Received : 17 June 19
Accepted : 19 June 19
Published : 11 October 19

DOI
10.25259/SNI_361_2019

Quick Response Code:

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.

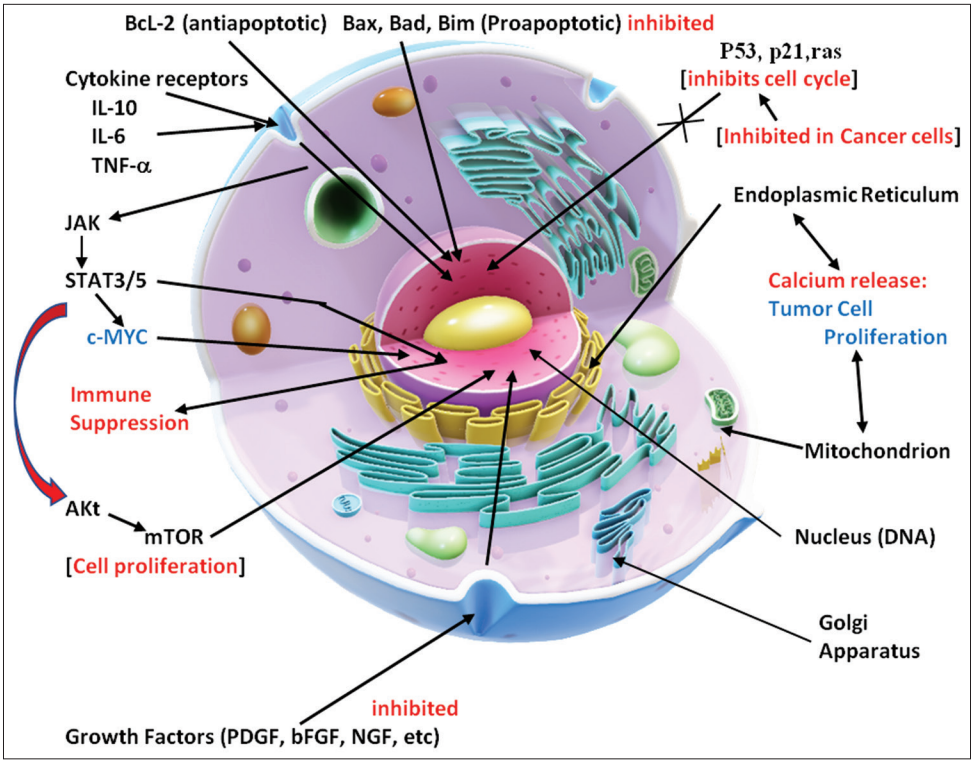


Figure 1: Simplified illustration of a cell, pointing out some of the important mechanisms of viral oncomodulation.

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

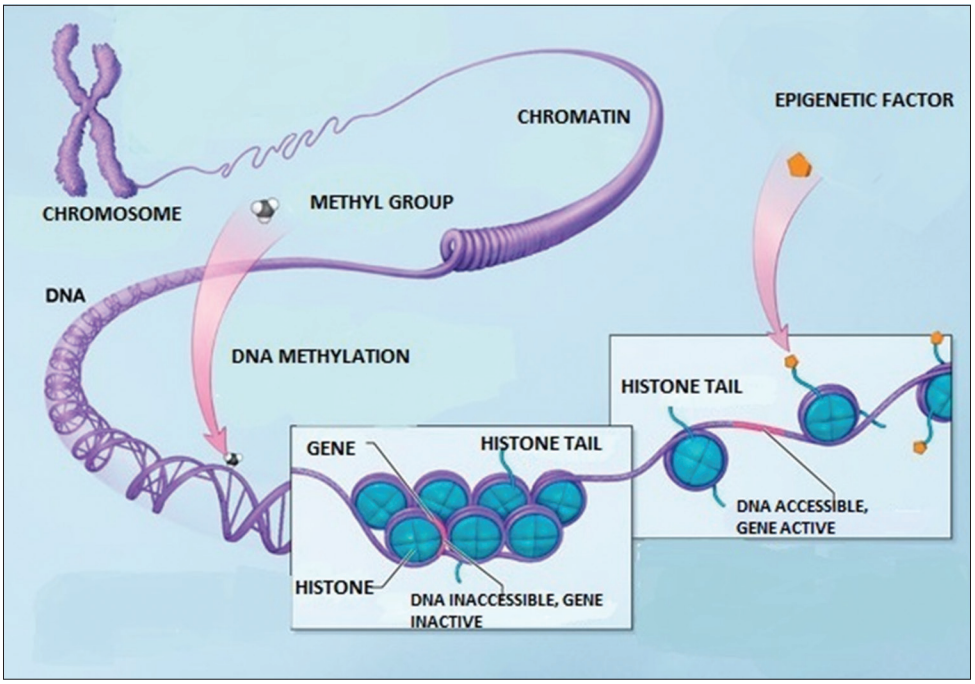


Figure 2: Illustration of epigenetic mechanisms, demonstrating the mechanisms by which environmental stimuli can affect DNA function.

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.[7,15,52,161] 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.[177] 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.[173-176]

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].

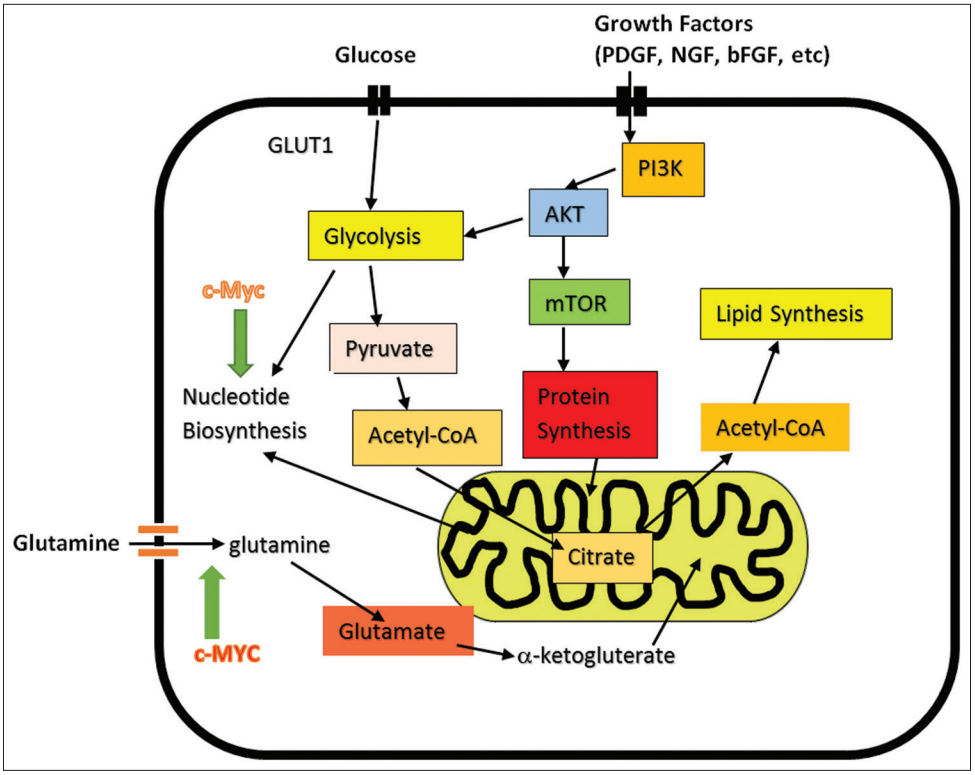


Figure 3: Cancer Cell Metabolism involving its two major fuels, glucose and glutamine. Demonstrates role of c-MYC in induction of glutamine addiction. Myc consist of a family of regulator genes (proto-oncogenes) coding for transcription factors. The Myc family consists of c-myc, l-myc and n-myc. Also demonstrates the influence of growth factors on cancer cell-signaling.

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].[97,99] Once the cancer transformation takes place, a number of mechanisms are activated to ensure cancer cell survival.[158] 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.[15,233] 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.[52,112,161]

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 exacting 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.[129,234] 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

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.[76,163]

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.[129]

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.[45,129] 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.[67] 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 mucoepidermoid 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.[156] 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.[142] 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.[64] 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.[77,144] 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.[44] In essence, it has been demonstrated that persistent viral infections are essential for oncomodulation.[44]

The latent virus may be inactive only in so far as viral reproduction and not production of the oncomodulatory proteins.[80,160] 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.[23,134]

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.[122] 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

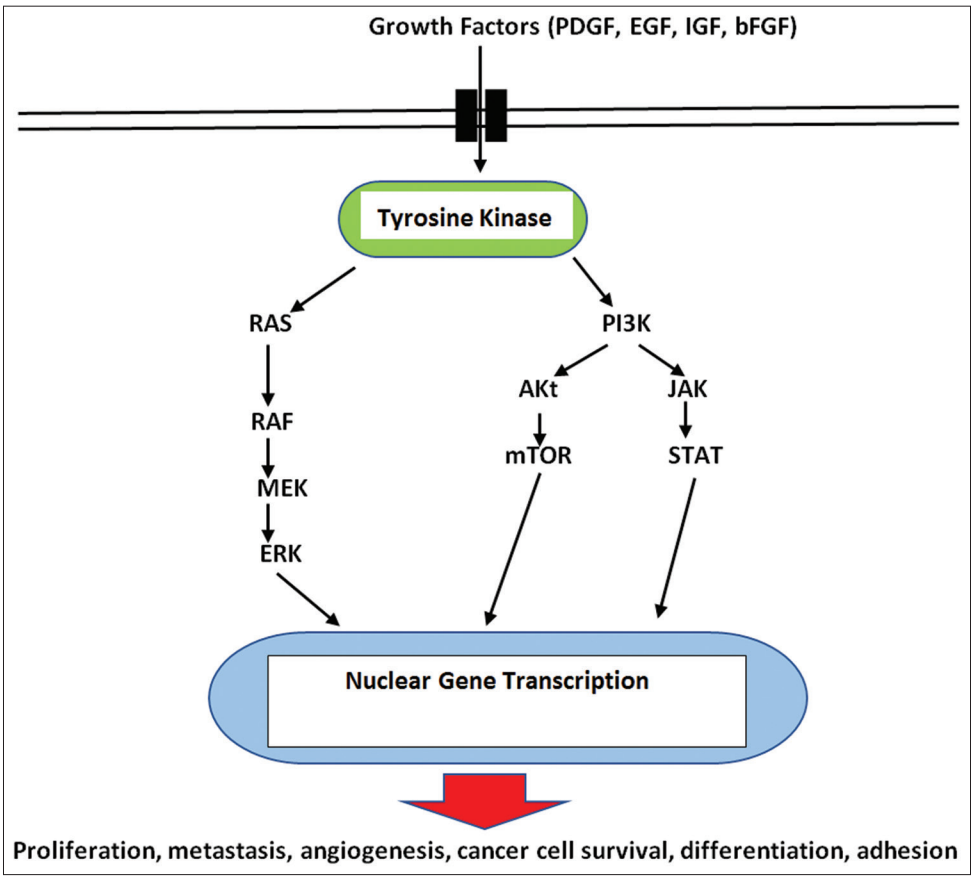
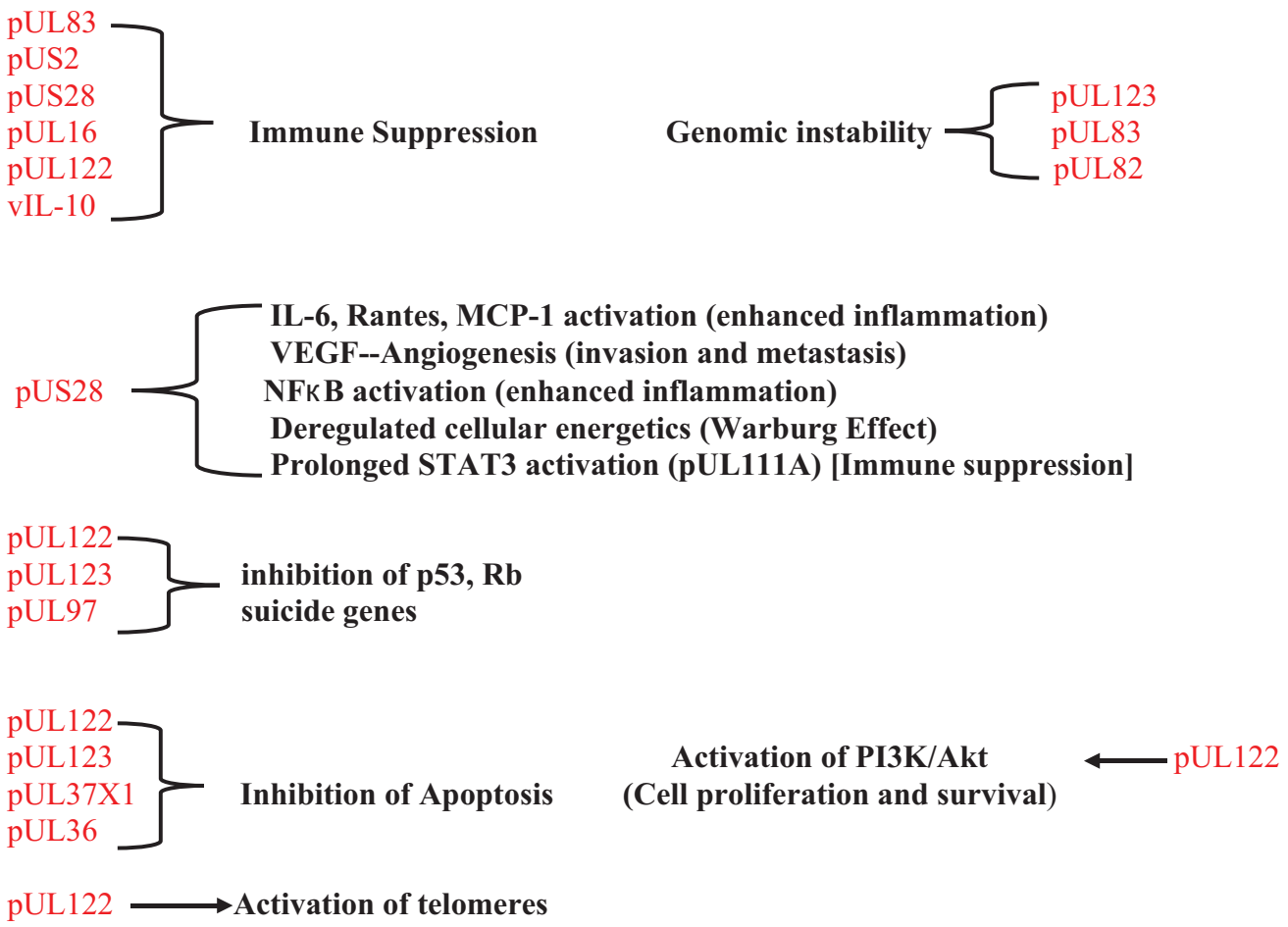


Figure 4: Growth factor involved in cell-signaling pathways.

Table 1: NCMV proteins and their oncogenic effects on cell mechanisms



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].[53]

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.[8] 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.[83,159] 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.[74] 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.[82] 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].[57,229]

High levels of IL-6 have been associated with a poor prognosis in several types of cancer [Figure 1].[181] 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

metalloproteinases (MMPs).[66] Another way HCMV enhances inflammation is by activation of NFκB, 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.[232] HCMV immediate early genes (IE) IE-1-72, IE-2, IE-2-86, and IE2-55 regulate NFκB activation.[232] NFκB is dramatically activated in most cancers [Figure 5].[7,16]

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.[44,185] 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.[2] 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.[17,149] 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

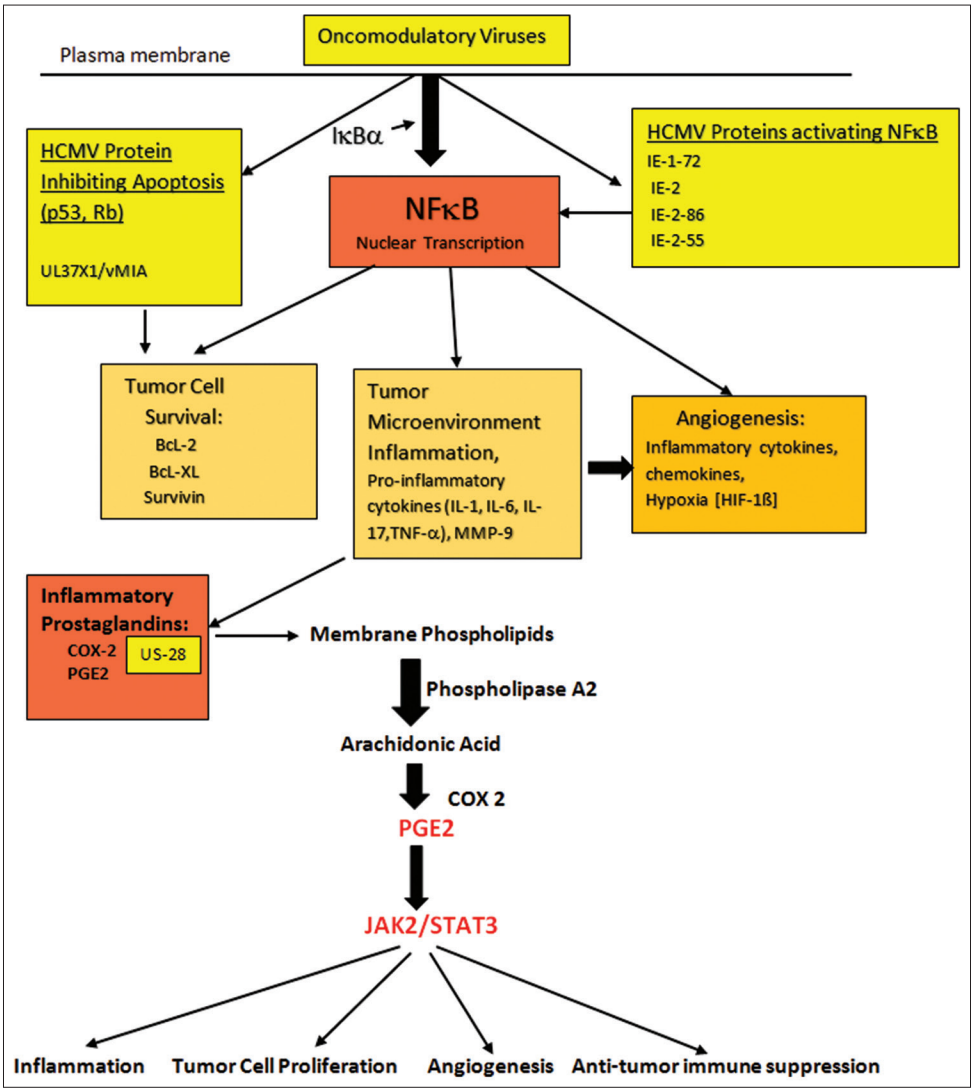


Figure 5: Activation of COX-2 leading to generation of prostaglandins (PGE2) and subsequent enhancement of inflammation. Tumor cell proliferation, angiogenesis and suppression of anti-tumor immune activity are enhanced in the face of tumor microenvironment inflammation. The central role played by NFκB, 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.[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.[132]

Another interesting link to cancer behavior is the finding that NFκB differentially regulates the oncogene promoter c-Myc.[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.[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.[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.[171] 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.[38] HCMV can persistently infect glioma cells and are reactivated by inflammation within the tumor microenvironment and with immunosuppression.[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.[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.[127,147]

HCMV virus has been shown to inhibit differentiation of stem cells into neurons but not astrocytes.[107,142] Susceptibility to HCMV infection declines with differentiation into neurons, but HCMV can infect mature astrocytes.[37] PDGF and its receptor are essential for stem cell self-renewal, and PDGF inhibits stem cell differentiation into neurons, astrocytes, and oligodendrocytes.[69] The PDGF ligand is a powerful stimulus for transformation of progenitors into malignant gliomas as seen with retroviruses expressing PDGF [Figure 4].[5] 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.[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.[78]

Both BMX kinase and IL-6 drive and maintain GSCs.[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.[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.[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.[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.[212] 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.[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.[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 nontumor 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 NASIDs 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.[68] 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.[101] 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.[55,227]

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.[36,125,145] 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].[113,138,183,204] 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]

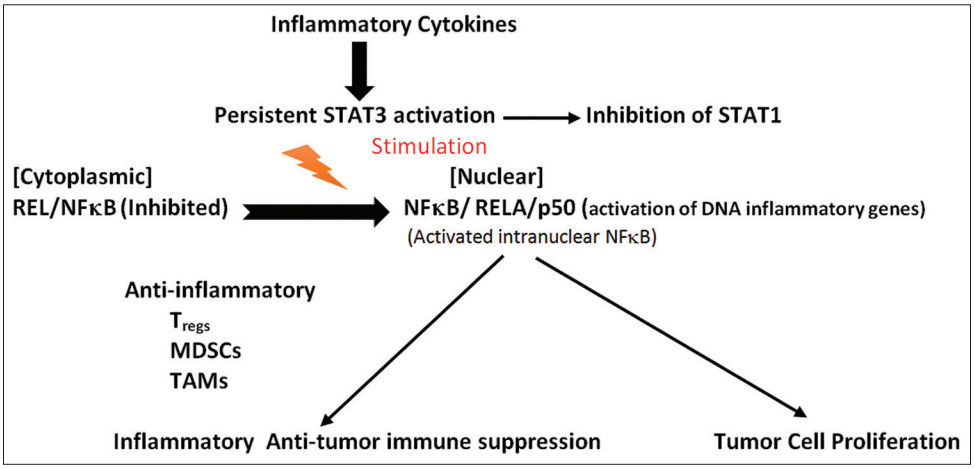


Figure 6: Demonstrating persistent activation of STAT3 by inflammatory cytokines within the tumor environment, which activates cytoplasmic REL/NFκB chronically. In combination, this suppresses anti-tumor immunity and stimulates tumor cell proliferation.

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.[54] COX-2, which is also downstream from NFκB, is involved in cancer inflammation and activates STAT3 through IL-6 [Figure 6].[54]

A number of inflammatory cytokines can activate STAT3 through NFκB/IL-6 signaling, including IL-17, IL-21, and IL-23.[39,143,216]

NFκB has a dual role in cancer, acting either an anticancer pathway or procancer pathway by regulating different sets of genes.[13,111] 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.[228]

The procarcinogenic factor RELA is persistently activated in tumor cells and tumor-associated immune cells and requires continuous activation of STAT3.[111] 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 [Figure 6].[88]

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].[32] 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.[219] 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.[9,218,219] This viral factor has potent antiapoptotic activity by binding to BAX apoptotic protein on the outer mitochondrial membrane (OMM).[218] 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.[214]

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.[219] 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.[150] E1B-19K protein also interacts with p53 to suppress mitochondrial-mediated apoptosis induced by p53.[41] Viruses encoded proteins can control cell suicide genes such as p53 and retinoblastoma proteins (Rb) [Figure 5].[234]

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.[44] 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.[46,199] 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.[200] It has also been shown that constitutional activation of hTERT is sufficient to immortalize normal diploid cells.[46]

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.[50] IE1 viral genome expression in malignant gliomas is positively correlated with the grade of the tumor with GBM having the highest levels.[170] This viral gene factor is also correlated with survival in glioblastoma patients.[186] HCMV IE1 gene is found in most tumors and causes proliferation of glioblastoma cells lines.[50]

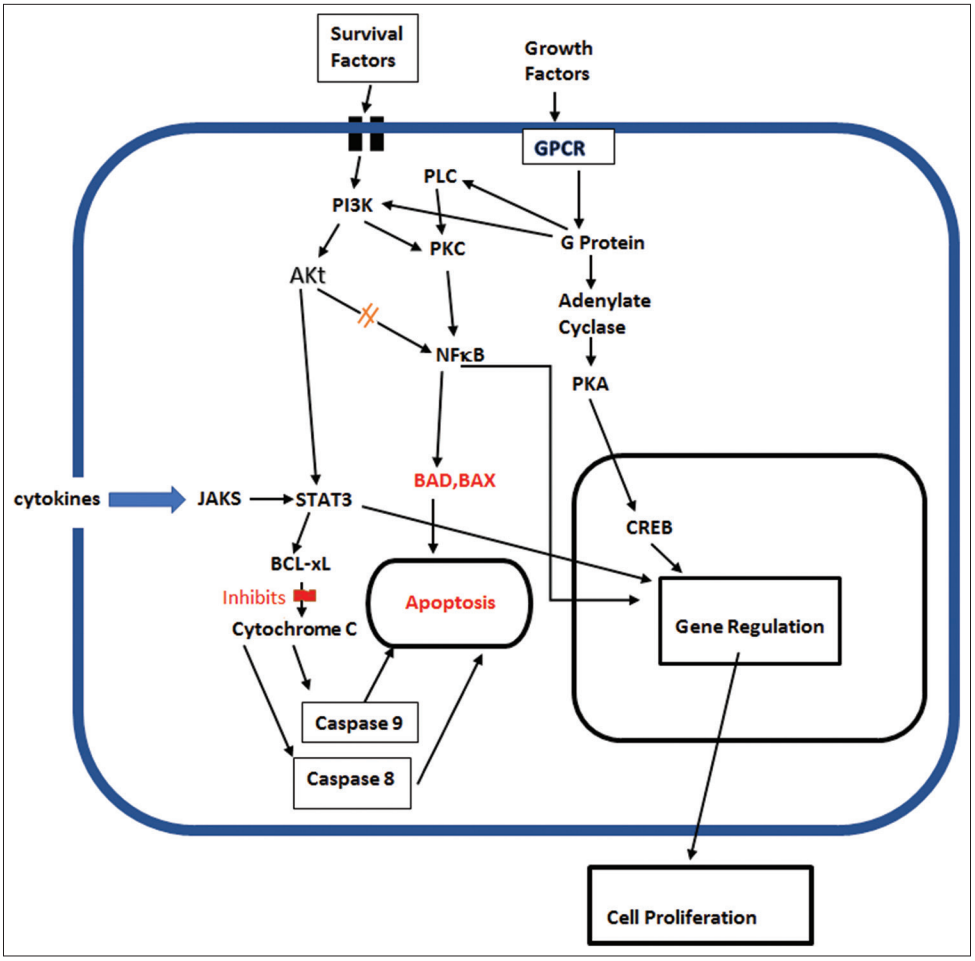


Figure 7: Induction of anti-apoptosis factors through JAK/STAT3 signaling, survival receptors and growth factor receptors.

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.[47] 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.[95] 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 [Figure 3].[92]

TUMOR ANGIOGENESIS INDUCED BY VIRAL PROTEINS

Angiogenesis begins very early in tumor growth.[30] 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.[29] Fibroblasts, near the tumor bed, also produce proangiogenic factors.[97,154] 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.[75] The hypoxic tumor microenvironment triggers the release of hypoxia-inducible factor (HIF)-1α from tumor cells, which upregulates several of these angiogenic factors.[172] 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.[224] Wnt and Notch signaling play a key role in the development of cancer stem cells and stemness maintenance.[98] 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.[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.[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.[100,120]

HCMV infections are characterized by a widespread presence of viruses in the vessel walls of major arteries throughout the body.[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.[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.[66] 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.[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.[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.[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.[152]

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.[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].[153] 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].[136] Moreover, as we saw in the case of cancer cells, a great deal of glycolysis is directed toward macromolecule synthesis.[136,137] This glycolysis switch increases the production of substrates for the biosynthesis of nucleotides, fatty acids, and lipid for viral reproduction.[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.[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.[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.[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.[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.[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

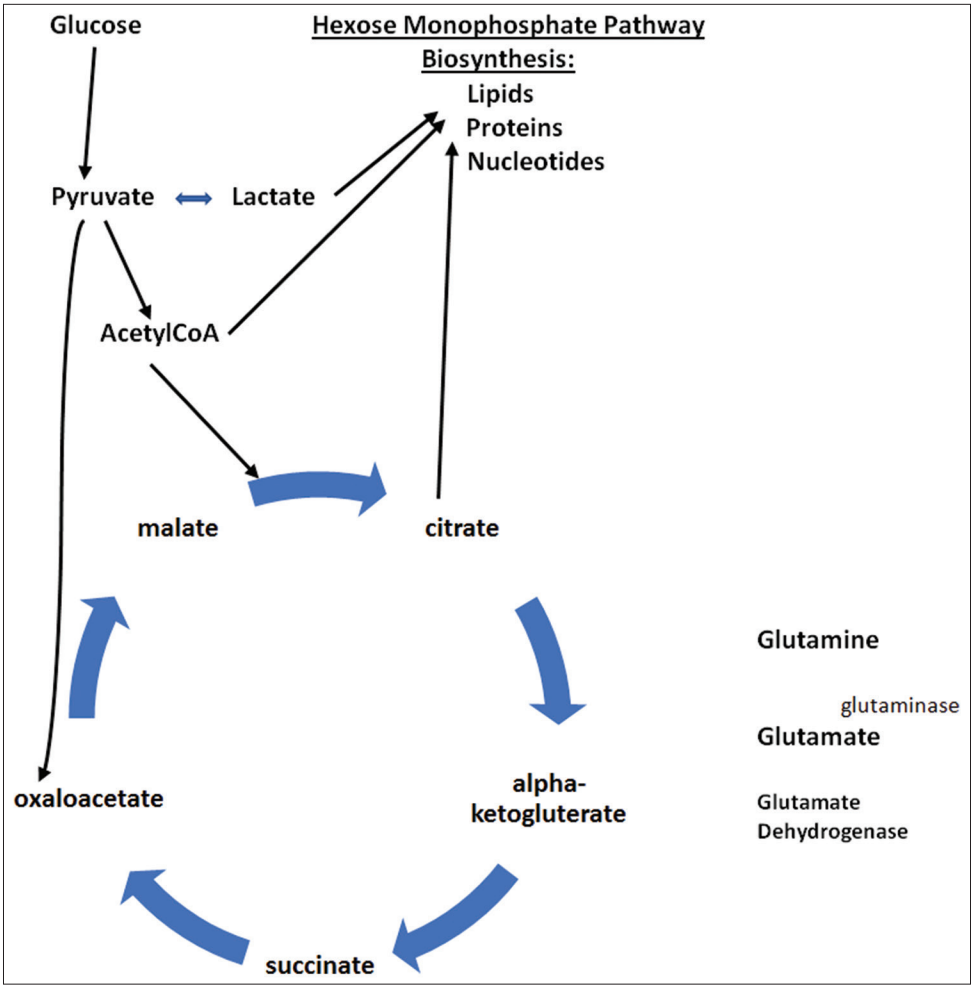


Figure 8: Warburg effect, altering cellular metabolism to maximize use of glycolysis and Kreb's cycle intermediates for biosynthesis of lipids, proteins and nucleotides for viral and cancer cell reproduction. Demonstrating glutaminolysis pathway for converting glutamine to glutamate and then to alpha-ketogluterate within Kreb's cycle, used for biosynthesis of substrates.

Krebs cycle, thus supplying metabolic intermediates for the Krebs pathway (anaplerosis) taking place in the mitochondria [Figure 8].[60,222] This is similar to what we see in tumor cell metabolism.[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.[137,231] c-Myc triggers a transcriptional program that promotes glutamine uptake and conversion to alpha-ketoglutarate, resulting in glutamine addiction.[222] Several studies have shown that c-Myc mRNA and protein levels are elevated in HCMV infections.[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.[60] Glioblastoma cells develop high rates of glutamine metabolism, which is the preferred source of carbon for biosynthesis of metabolic intermediates.[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.[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.[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.[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.[26,33,96,103,110] In a recent study of breast cancers, serum levels of glutamate, but not glutamine or lactate, were elevated in tumor-bearing animals over time.[65] 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.[115,178] 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.[31] Another study confirmed that glutamate plays a major role in activating the MMP system.[65] 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.[65] 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.[220] 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.[225] It is known that medulloblastomas with overactivation of c-Myc have the poorest prognosis.[225] 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.[226] 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.[90,118,141] 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.[118,164]

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.[198] Selected metabotropic glutamate receptors are also linked to proliferation, differentiation, and tumor survival in neural tumors, which include medulloblastomas and high-grade gliomas.[89,141] Ectopic expression of glutamatergic mGluR1 in normal melanocytes has been shown to cause hyperproliferation and transformation to malignant tumors.[123,141]

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.[56] 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

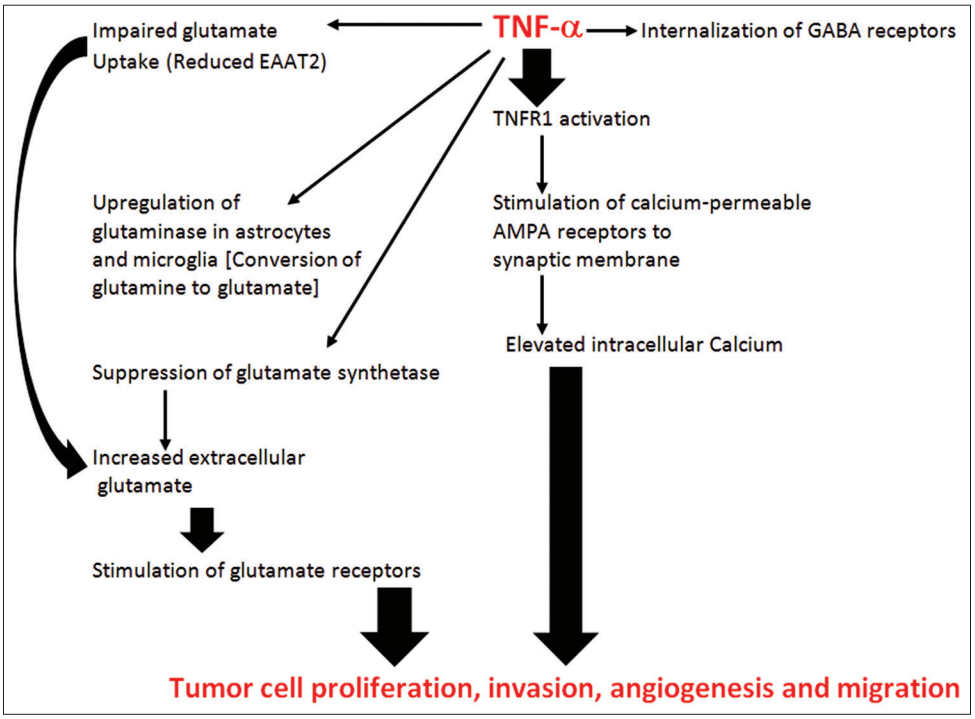


Figure 9: Immunoexcitotoxicity: Effect of TNF-alpha on trafficking of calcium-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors to synapse and mechanism for elevation of extracellular glutamate levels resulting in enhanced aggressiveness of tumors.

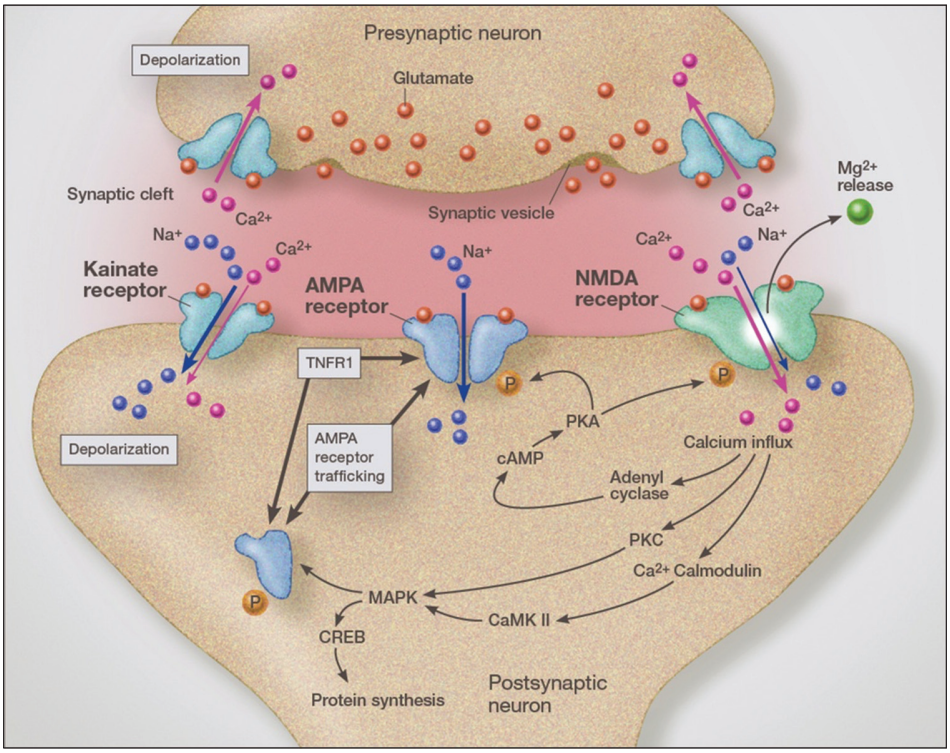


Figure 10: Glutamate receptors with trafficking of calcium-permeable AMPA receptors to synaptic cleft induced by inflammatory cytokine TNF-alpha activation of TNFR1 receptor activation. Oncomodulatory viruses induce high levels of TNF-alpha.

Table 2: Lonotropic glutamate receptors and their assigned subunits. In parentheses is the older nomenclature

Glutamate receptor family	Subunits (Older nomenclature)
AMPA	GluA1 (GluR1)
	GluA2 (GluR2)
	GluA3 (GluR3)
	GluA4 (GluR4)
Kainate	GluK1 (GluR5)
	GluK2 (GluR6)
	GluK3 (GluR7))
	GluK4 (KA-1)
	GluK5 (KA-2)
NMDA	GluN1 (NR1)
	GluN2A (NR2A)
	GluN2B (NR2B)
	GluN2C (NR2C)
	GluN2D (NR2D)
	GluN3A (NR3A)

Table 3: Metabotropic glutamate receptor subunits. Group I through 3

Metabotropic glutamate receptors	
Group I	mGluR1
	mGluR5
Group II	mGluR 2
	mGluR3
Group III	mGluR4
	mGluR6
	mGluR7
	mGluR8

vaccine development as a number of vaccines contain viral components as contaminants, including viral proteins.[201,211]

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*.[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.[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.[165,202,208,215] Several natural compounds also inhibit immunoexcitotoxicity and can lower glutamate levels.[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.[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.[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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ahn SH, Kim HJ, Jeong I, Hong YJ, Kim MJ, Rhie DJ, *et al.* Grape seed proanthocyanidin extract inhibits glutamate-induced cell death through inhibition of calcium signals and nitric oxide formation in cultured rat hippocampal neurons. BMC Neurosci 2011;12:78.
2. Anzil AP, Stavrou D, Blizinger K. Type-C viral particles in cell cultures of chemically induced glioma in Sprague-Dawley rats. Vopr Onkol 1978;24:30-2.
3. Arena A, Liberto MC, Iannello D, Capozza AB, Focà A. Altered cytokine production after human herpes virus Type 6 infection. New Microbiol 1999;22:293-300.
4. Arredondo J, Chernyavsky AI, Jolkovsky DL, Pinkerton KE, Grando SA. Receptor-mediated tobacco toxicity: Cooperation of the ras/Raf-1/MEK1/ERK and JAK-2/STAT-3 pathways downstream of alpha7 nicotinic receptor in oral keratinocytes. FASEB J 2006;20:2093-101.
5. Assanah M, Lochhead R, Ogden A, Bruce J, Goldman J, Canoll P, *et al.* Glial progenitors in adult white matter are driven to form malignant gliomas by platelet-derived growth factor-expressing retroviruses. J Neurosci 2006;26:6781-90.
6. Ayala FR, Rocha RM, Carvalho KC, Carvalho AL, da Cunha IW, Lourenço SV, *et al.* GLUT1 and GLUT3 as potential prognostic markers for oral squamous cell carcinoma. Molecules 2010;15:2374-87.
7. Balkwill F, Mantovani A. Inflammation and cancer: Back to Virchow? Lancet 2001;357:539-45.
8. Balkwill FR, Capasso M, Hagemann T. The tumor microenvironment at a glance. J Cell Sci 2012;125:5591-6.
9. Barami K. Oncomodulatory mechanisms of human cytomegalovirus in gliomas. J Clin Neurosci 2010;17:819-23.
10. Bardell D, Essex M. Glycolysis during early infection of feline and human cells with feline leukemia virus. Infect Immun 1974;9:824-7.
11. Baryawno N, Rahbar A, Wolmer-Solberg N, Taher C, Odeberg J, Darabi A, *et al.* Detection of human cytomegalovirus in medulloblastomas reveals a potential therapeutic target. J Clin Invest 2011;121:4043-55.
12. Baryawno N, Sveinbjörnsson B, Kogner P, Johnsen JI. Medulloblastoma: A disease with disorganized developmental signaling cascades. Cell Cycle 2010;9:2548-54.
13. Baud V, Karin M. Is NF-kappaB a good target for cancer therapy? Hopes and pitfalls. Nat Rev Drug Discov 2009;8:33-40.
14. Becker JC, Andersen MH, Schrama D, Thor Straten P. Immune-suppressive properties of the tumor microenvironment. Cancer Immunol Immunother 2013;62:1137-48.
15. Ben-Baruch A. Inflammation-associated immune suppression in cancer: The roles played by cytokines, chemokines and additional mediators. Semin Cancer Biol 2006;16:38-52.
16. Ben-Neriah Y, Karin M. Inflammation meets cancer, with NF-κB as the matchmaker. Nat Immunol 2011;12:715-23.
17. Bentvelzen P. Host-virus interactions in murine mammary carcinogenesis. Biochim Biophys Acta 1974;355:236-59.
18. Blaylock RL, Maroon J. Natural plant products and extracts that reduce immunoexcitotoxicity-associated neurodegeneration and promote repair within the central nervous system. Surg Neurol Int 2012;3:19.
19. Blaylock RL. Cancer microenvironment, inflammation and cancer stem cells: A hypothesis for a paradigm change and new targets in cancer control. Surg Neurol Int 2015;6:92.
20. Boldogh I, AbuBakar S, Albrecht T. Activation of proto-oncogenes: An immediate early event in human

cytomegalovirus infection. Science 1990;247:561-4.
21. Boldogh I, AbuBakar S, Deng CZ, Albrecht T. Transcriptional activation of cellular oncogenes fos, jun, and myc by human cytomegalovirus. J Virol 1991;65:1568-71.
22. Bollrath J, Phesse TJ, von Burstin VA, Putoczki T, Bennecke M, Bateman T, *et al.* Gp130-mediated stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. Cancer Cell 2009;15:91-102.
23. Bresnahan WA, Hultman GE, Shenk T. Replication of wild-type and mutant human cytomegalovirus in life-extended human diploid fibroblasts. J Virol 2000;74:10816-8.
24. Britt WJ, Mach M. Human cytomegalovirus glycoproteins. Intervirology 1996;39:401-12.
25. Brocke KS, Staufner C, Luksch H, Geiger KD, Stepulak A, Marzahn J, *et al.* Glutamate receptors in pediatric tumors of the central nervous system. Cancer Biol Ther 2010;9:455-68.
26. Budczies J, Pfitzner BM, Györffy B, Winzer KJ, Radke C, Dietel M, *et al.* Glutamate enrichment as new diagnostic opportunity in breast cancer. Int J Cancer 2015;136:1619-28.
27. Butel JS. Viral carcinogenesis: Revelation of molecular mechanisms and etiology of human disease. Carcinogenesis 2000;21:405-26.
28. Caposio P, Orloff SL, Streblow DN. The role of cytomegalovirus in angiogenesis. Virus Res 2011;157:204-11.
29. Carmeliet P, Dor Y, Herbert JM, Fukumura D, Brusselmans K, Dewerchin M, *et al.* Role of HIF-1alpha in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. Nature 1998;394:485-90.
30. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature 2000;407:249-57.
31. Castro-Castro A, Marchesin V, Monteiro P, Lodillinsky C, Rossé C, Chavrier P, *et al.* Cellular and molecular mechanisms of MT1-MMP-dependent cancer cell invasion. Annu Rev Cell Dev Biol 2016;32:555-76.
32. Catlett-Falcone R, Landowski TH, Oshiro MM, Turkson J, Levitzki A, Savino R, *et al.* Constitutive activation of stat3 signaling confers resistance to apoptosis in human U266 myeloma cells. Immunity 1999;10:105-15.
33. Cavalheiro EA, Olney JW. Glutamate antagonists: Deadly liaisons with cancer. Proc Natl Acad Sci U S A 2001;98:5947-8.
34. Chambers JW, Maguire TG, Alwine JC. Glutamine metabolism is essential for human cytomegalovirus infection. J Virol 2010;84:1867-73.
35. Chan G, Bivins-Smith ER, Smith MS, Yurochko AD. Transcriptome analysis of NF-kappaB- and phosphatidylinositol 3-kinase-regulated genes in human cytomegalovirus-infected monocytes. J Virol 2008;82:1040-6.
36. Chan KS, Sano S, Kiguchi K, Anders J, Komazawa N, Takeda J, *et al.* Disruption of stat3 reveals a critical role in both the initiation and the promotion stages of epithelial carcinogenesis. J Clin Invest 2004;114:720-8.
37. Cheeran MC, Hu S, Ni HT, Sheng W, Palmquist JM, Peterson PK, *et al.* Neural precursor cell susceptibility to human cytomegalovirus diverges along glial or neuronal differentiation pathways. J Neurosci Res 2005;82:839-50.
38. Cheeran MC, Hu S, Yager SL, Gekker G, Peterson PK, Lokensgard JR, *et al.* Cytomegalovirus induces cytokine and chemokine production differentially in microglia and astrocytes: Antiviral implications. J Neurovirol 2001;7:135-47.
39. Chen Z, O'Shea JJ. Th17 cells: A new fate for differentiating helper T cells. Immunol Res 2008;41:87-102.
40. Cheng F, Wang HW, Cuenca A, Huang M, Ghansah T, Brayer J, *et al.* A critical role for stat3 signaling in immune tolerance. Immunity 2003;19:425-36.
41. Chiou SK, Tseng CC, Rao L, White E. Functional complementation of the adenovirus E1B 19-kilodalton protein with bcl-2 in the inhibition of apoptosis in infected cells. J Virol 1994;68:6553-66.
42. Choe G, Horvath S, Cloughesy TF, Crosby K, Seligson D, Palotie A, *et al.* Analysis of the phosphatidylinositol 3'-kinase signaling pathway in glioblastoma patients *in vivo*. Cancer Res 2003;63:2742-6.
43. Cinatl J Jr., Bittoova M, Margraf S, Vogel JU, Cinatl J, Preiser W, *et al.* Cytomegalovirus infection decreases expression of thrombospondin-1 and -2 in cultured human retinal glial cells: Effects of antiviral agents. J Infect Dis 2000;182:643-51.
44. Cinatl J Jr., Cinatl J, Vogel JU, Kotchetkov R, Driever PH, Kabickova H, *et al.* Persistent human cytomegalovirus infection induces drug resistance and alteration of programmed cell death in human neuroblastoma cells. Cancer Res 1998;58:367-72.
45. Cinatl J Jr., Cinatl J, Vogel JU, Rabenau H, Kornhuber B, Doerr HW, *et al.* Modulatory effects of human cytomegalovirus infection on malignant properties of cancer cells. Intervirology 1996;39:259-69.
46. Cinatl J Jr., Nevels M, Paulus C, Michaelis M. Activation of telomerase in glioma cells by human cytomegalovirus: Another piece of the puzzle. J Natl Cancer Inst 2009;101:441-3.
47. Cinatl J Jr., Vogel JU, Kotchetkov R, Wilhelm Doerr H. Oncomodulatory signals by regulatory proteins encoded by human cytomegalovirus: A novel role for viral infection in tumor progression. FEMS Microbiol Rev 2004;28:59-77.
48. Cobbs CS, Brenman JE, Aldape KD, Bredt DS, Israel MA. Expression of nitric oxide synthase in human central nervous system tumors. Cancer Res 1995;55:727-30.
49. Cobbs CS, Harkins L, Samanta M, Gillespie GY, Bharara S, King PH, *et al.* Human cytomegalovirus infection and expression in human malignant glioma. Cancer Res 2002;62:3347-50.
50. Cobbs CS, Soroceanu L, Denham S, Zhang W, Kraus MH. Modulation of oncogenic phenotype in human glioma cells by cytomegalovirus IE1-mediated mitogenicity. Cancer Res 2008;68:724-30.
51. Cobbs CS. Evolving evidence implicates cytomegalovirus as a promoter of malignant glioma pathogenesis. Herpesviridae 2011;2:10.
52. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860-7.
53. Coussens LM, Zitvogel L, Palucka AK. Neutralizing tumor-promoting chronic inflammation: A magic bullet? Science 2013;339:286-91.
54. Dalwadi H, Krysan K, Heuze-Vourc'h N, Dohadwala M, Elashoff D, Sharma S, *et al.* Cyclooxygenase-2-dependent activation of signal transducer and activator of transcription 3

by interleukin-6 in non-small cell lung cancer. Clin Cancer Res 2005;11:7674-82.
55. Darnell JE Jr. Transcription factors as targets for cancer therapy. Nat Rev Cancer 2002;2:740-9.
56. de Groot JF, Liu TJ, Fuller G, Yung WK. The excitatory amino acid transporter-2 induces apoptosis and decreases glioma growth *in vitro* and *in vivo*. Cancer Res 2005;65:1934-40.
57. de la Iglesia N, Puram SV, Bonni A. STAT3 regulation of glioblastoma pathogenesis. Curr Mol Med 2009;9:580-90.
58. De Leo A, Arena G, Lacanna E, Oliviero G, Colavita F, Mattia E, *et al.* Resveratrol inhibits epstein barr virus lytic cycle in burkitt's lymphoma cells by affecting multiple molecular targets. Antiviral Res 2012;96:196-202.
59. de Wit RH, Mujić-Delić A, van Senten JR, Fraile-Ramos A, Siderius M, Smit MJ, *et al.* Human cytomegalovirus encoded chemokine receptor US28 activates the HIF-1α/PKM2 axis in glioblastoma cells. Oncotarget 2016;7:67966-85.
60. DeBerardinis RJ, Mancuso A, Daikhin E, Nissim I, Yudkoff M, Wehrli S, *et al.* Beyond aerobic glycolysis: Transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. Proc Natl Acad Sci U S A 2007;104:19345-50.
61. Deng W, Rosenberg PA, Volpe JJ, Jensen FE. Calcium-permeable AMPA/kainate receptors mediate toxicity and preconditioning by oxygen-glucose deprivation in oligodendrocyte precursors. Proc Natl Acad Sci U S A 2003;100:6801-6.
62. Dillon RL, Muller WJ. Distinct biological roles for the akt family in mammary tumor progression. Cancer Res 2010;70:4260-4.
63. Din FV, Theodoratou E, Farrington SM, Tenesa A, Barnetson RA, Cetnarskyj R, *et al.* Effect of aspirin and NSAIDs on risk and survival from colorectal cancer. Gut 2010;59:1670-9.
64. Dolan A, Cunningham C, Hector RD, Hassan-Walker AF, Lee L, Addison C, *et al.* Genetic content of wild-type human cytomegalovirus. J Gen Virol 2004;85:1301-12.
65. Dornier E, Rabas N, Mitchell L, Novo D, Dhayade S, Marco S, *et al.* Glutaminolysis drives membrane trafficking to promote invasiveness of breast cancer cells. Nat Commun 2017;8:2255.
66. Dumortier J, Streblow DN, Moses AV, Jacobs JM, Kreklywich CN, Camp D, *et al.* Human cytomegalovirus secretome contains factors that induce angiogenesis and wound healing. J Virol 2008;82:6524-35.
67. Dziurzynski K, Chang SM, Heimberger AB, Kalejta RF, McGregor Dallas SR, Smit M, *et al.* Consensus on the role of human cytomegalovirus in glioblastoma. Neuro Oncol 2012;14:246-55.
68. Dziurzynski K, Wei J, Qiao W, Hatiboglu MA, Kong LY, Wu A, *et al.* Glioma-associated cytomegalovirus mediates subversion of the monocyte lineage to a tumor propagating phenotype. Clin Cancer Res 2011;17:4642-9.
69. Erlandsson A, Brännvall K, Gustafsdottir S, Westermark B, Forsberg-Nilsson K. Autocrine/paracrine platelet-derived growth factor regulates proliferation of neural progenitor cells. Cancer Res 2006;66:8042-8.
70. Evers DL, Chao CF, Wang X, Zhang Z, Huong SM, Huang ES, *et al.* Human cytomegalovirus-inhibitory flavonoids: Studies on antiviral activity and mechanism of action. Antiviral Res 2005;68:124-34.
71. Evers DL, Wang X, Huong SM, Huang DY, Huang ES. 3,4',5-trihydroxy-trans-stilbene (resveratrol) inhibits human cytomegalovirus replication and virus-induced cellular signaling. Antiviral Res 2004;63:85-95.
72. Fantin VR, St-Pierre J, Leder P. Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. Cancer Cell 2006;9:425-34.
73. Fenske W, Völker HU, Adam P, Hahner S, Johanssen S, Wortmann S, *et al.* Glucose transporter GLUT1 expression is an stage-independent predictor of clinical outcome in adrenocortical carcinoma. Endocr Relat Cancer 2009;16:919-28.
74. Fiallos E, Judkins J, Matlaf L, Prichard M, Dittmer D, Cobbs C, *et al.* Human cytomegalovirus gene expression in long-term infected glioma stem cells. PLoS One 2014;9:e116178.
75. Folkman J, Browder T, Palmblad J. Angiogenesis research: Guidelines for translation to clinical application. Thromb Haemost 2001;86:23-33.
76. Fortunato EA, McElroy AK, Sanchez I, Spector DH. Exploitation of cellular signaling and regulatory pathways by human cytomegalovirus. Trends Microbiol 2000;8:111-9.
77. Furukawa T. A variant of human cytomegalovirus derived from a persistently infected culture. Virology 1984;137:191-4.
78. Galli R, Binda E, Orfanelli U, Cipelletti B, Gritti A, De Vitis S, *et al.* Isolation and characterization of tumorigenic, stem-like neural precursors from human glioblastoma. Cancer Res 2004;64:7011-21.
79. Ghandadi M, Sahebkar A. Curcumin: An effective inhibitor of interleukin-6. Curr Pharm Des 2017;23:921-31.
80. Gires O, Kohlhuber F, Kilger E, Baumann M, Kieser A, Kaiser C, *et al.* Latent membrane protein 1 of epstein-barr virus interacts with JAK3 and activates STAT proteins. EMBO J 1999;18:3064-73.
81. Grivennikov S, Karin E, Terzic J, Mucida D, Yu GY, Vallabhapurapu S, *et al.* IL-6 and stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell 2009;15:103-13.
82. Guryanova OA, Wu Q, Cheng L, Lathia JD, Huang Z, Yang J, *et al.* Nonreceptor tyrosine kinase BMX maintains self-renewal and tumorigenic potential of glioblastoma stem cells by activating STAT3. Cancer Cell 2011;19:498-511.
83. Hargett D, Shenk TE. Experimental human cytomegalovirus latency in CD14+ monocytes. Proc Natl Acad Sci U S A 2010;107:20039-44.
84. Harkins L, Volk AL, Samanta M, Mikolaenko I, Britt WJ, Bland KI, *et al.* Specific localisation of human cytomegalovirus nucleic acids and proteins in human colorectal cancer. Lancet 2002;360:1557-63.
85. Harkins LE, Matlaf LA, Soroceanu L, Klemm K, Britt WJ, Wang W, *et al.* Detection of human cytomegalovirus in normal and neoplastic breast epithelium. Herpesviridae 2010;1:8.
86. Heinrich PC, Behrmann I, Müller-Newen G, Schaper F, Graeve L. Interleukin-6-type cytokine signalling through the gp130/Jak/STAT pathway. Biochem J 1998;334 (Pt 2):297-314.
87. Hendrix MG, Dormans PH, Kitslaar P, Bosman F,

Bruggeman CA. The presence of cytomegalovirus nucleic acids in arterial walls of atherosclerotic and nonatherosclerotic patients. Am J Pathol 1989;134:1151-7.
88. Ho HH, Ivashkiv LB. Role of STAT3 in Type I interferon responses. Negative regulation of STAT1-dependent inflammatory gene activation. J Biol Chem 2006;281:14111-8.
89. Iacovelli L, Arcella A, Battaglia G, Pazzaglia S, Aronica E, Spinsanti P, *et al.* Pharmacological activation of mGlu4 metabotropic glutamate receptors inhibits the growth of medulloblastomas. J Neurosci 2006;26:8388-97.
90. Ishiuchi S, Tsuzuki K, Yoshida Y, Yamada N, Hagimura N, Okado H, *et al.* Blockage of ca(2+)-permeable AMPA receptors suppresses migration and induces apoptosis in human glioblastoma cells. Nat Med 2002;8:971-8.
91. Ishiuchi S, Yoshida Y, Sugawara K, Aihara M, Ohtani T, Watanabe T, *et al.* Ca2+-permeable AMPA receptors regulate growth of human glioblastoma via akt activation. J Neurosci 2007;27:7987-8001.
92. Itoh N, Semba S, Ito M, Takeda H, Kawata S, Yamakawa M, *et al.* Phosphorylation of akt/PKB is required for suppression of cancer cell apoptosis and tumor progression in human colorectal carcinoma. Cancer 2002;94:3127-34.
93. Ivashkiv LB. Inflammatory signaling in macrophages: Transitions from acute to tolerant and alternative activation states. Eur J Immunol 2011;41:2477-81.
94. Johnsen JI, Baryawno N, Söderberg-Nauclér C. Is human cytomegalovirus a target in cancer therapy? Oncotarget 2011;2:1329-38.
95. Johnson RA, Wang X, Ma XL, Huong SM, Huang ES. Human cytomegalovirus up-regulates the phosphatidylinositol 3-kinase (PI3-K) pathway: Inhibition of PI3-K activity inhibits viral replication and virus-induced signaling. J Virol 2001;75:6022-32.
96. Kalariti N, Pissimissis N, Koutsilieris M. The glutamatergic system outside the CNS and in cancer biology. Expert Opin Investig Drugs 2005;14:1487-96.
97. Kalluri R, Zeisberg M. Fibroblasts in cancer. Nat Rev Cancer 2006;6:392-401.
98. Kamdje AH, Kamga PT, Simo RT, Vecchio L, Etet PF, Muller JM, *et al.* Developmental pathways associated with cancer metastasis: Notch, wnt, and hedgehog. Cancer Biol Med 2017;14:109-20.
99. Kastan MB, Canman CE, Leonard CJ. P53, cell cycle control and apoptosis: Implications for cancer. Cancer Metastasis Rev 1995;14:3-15.
100. Kazuno M, Tokunaga T, Oshika Y, Tanaka Y, Tsugane R, Kijima H, *et al.* Thrombospondin-2 (TSP2) expression is inversely correlated with vascularity in glioma. Eur J Cancer 1999;35:502-6.
101. Kim R, Emi M, Tanabe K, Arihiro K. Tumor-driven evolution of immunosuppressive networks during malignant progression. Cancer Res 2006;66:5527-36.
102. Kofman A, Marcinkiewicz L, Dupart E, Lyshchev A, Martynov B, Ryndin A, *et al.* The roles of viruses in brain tumor initiation and oncomodulation. J Neurooncol 2011;105:451-66.
103. Koochekpour S, Majumdar S, Azabdaftari G, Attwood K, Scioneaux R, Subramani D, *et al.* Serum glutamate levels correlate with gleason score and glutamate blockade decreases proliferation, migration, and invasion and induces apoptosis in prostate cancer cells. Clin Cancer Res 2012;18:5888-901.
104. Kortylewski M, Kujawski M, Herrmann A, Yang C, Wang L, Liu Y, *et al.* Toll-like receptor 9 activation of signal transducer and activator of transcription 3 constrains its agonist-based immunotherapy. Cancer Res 2009;69:2497-505.
105. Kortylewski M, Kujawski M, Wang T, Wei S, Zhang S, Pilon-Thomas S, *et al.* Inhibiting stat3 signaling in the hematopoietic system elicits multicomponent antitumor immunity. Nat Med 2005;11:1314-21.
106. Kortylewski M, Xin H, Kujawski M, Lee H, Liu Y, Harris T, *et al.* Regulation of the IL-23 and IL-12 balance by stat3 signaling in the tumor microenvironment. Cancer Cell 2009;15:114-23.
107. Kosugi I, Kawasaki H, Arai Y, Tsutsui Y. Innate immune responses to cytomegalovirus infection in the developing mouse brain and their evasion by virus-infected neurons. Am J Pathol 2002;161:919-28.
108. La Rosa FA, Pierce JW, Sonenshein GE. Differential regulation of the c-Myc oncogene promoter by the NF-kappa B rel family of transcription factors. Mol Cell Biol 1994;14:1039-44.
109. Lau SK, Chen YY, Chen WG, Diamond DJ, Mamelak AN, Zaia JA, *et al.* Lack of association of cytomegalovirus with human brain tumors. Mod Pathol 2005;18:838-43.
110. Le MN, Chan JL, Rosenberg SA, Nabatian AS, Merrigan KT, Cohen-Solal KA, *et al.* The glutamate release inhibitor riluzole decreases migration, invasion, and proliferation of melanoma cells. J Invest Dermatol 2010;130:2240-9.
111. Lee H, Herrmann A, Deng JH, Kujawski M, Niu G, Li Z, *et al.* Persistently activated stat3 maintains constitutive NF-kappaB activity in tumors. Cancer Cell 2009;15:283-93.
112. Leibovici D, Grossman HB, Dinney CP, Millikan RE, Lerner S, Wang Y, *et al.* Polymorphisms in inflammation genes and bladder cancer: From initiation to recurrence, progression, and survival. J Clin Oncol 2005;23:5746-56.
113. Lepiller Q, Abbas W, Kumar A, Tripathy MK, Herbein G. HCMV activates the IL-6-JAK-STAT3 axis in hepG2 cells and primary human hepatocytes. PLoS One 2013;8:e59591.
114. Li C, Allen A, Kwagh J, Doliba NM, Qin W, Najafi H, *et al.* Green tea polyphenols modulate insulin secretion by inhibiting glutamate dehydrogenase. J Biol Chem 2006;281:10214-21.
115. Lo M, Wang YZ, Gout PW. The x(c)- cystine/glutamate antiporter: A potential target for therapy of cancer and other diseases. J Cell Physiol 2008;215:593-602.
116. López-Ocejo O, Viloria-Petit A, Bequet-Romero M, Mukhopadhyay D, Rak J, Kerbel RS, *et al.* Oncogenes and tumor angiogenesis: The HPV-16 E6 oncoprotein activates the vascular endothelial growth factor (VEGF) gene promoter in a p53 independent manner. Oncogene 2000;19:4611-20.
117. Lv Y, Lei N, Wang D, An Z, Li G, Han F, *et al.* Protective effect of curcumin against cytomegalovirus infection in balb/c mice. Environ Toxicol Pharmacol 2014;37:1140-7.
118. Lyons SA, Chung WJ, Weaver AK, Ogunrinu T, Sontheimer H. Autocrine glutamate signaling promotes glioma cell invasion. Cancer Res 2007;67:9463-71.
119. Ma HI, Chiou SH, Hueng DY, Tai LK, Huang PI, Kao CL, *et al.* Celecoxib and radioresistant glioblastoma-derived CD133+ cells: Improvement in radiotherapeutic effects. Laboratory investigation. J Neurosurg 2011;114:651-62.

120. Maeda K, Nishiguchi Y, Kang SM, Yashiro M, Onoda N, Sawada T, *et al.* Expression of thrombospondin-1 inversely correlated with tumor vascularity and hematogenous metastasis in colon cancer. Oncol Rep 2001;8:763-6.
121. Maghazachi AA. Intracellular signaling events at the leading edge of migrating cells. Int J Biochem Cell Biol 2000;32:931-43.
122. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436-44.
123. Marín YE, Chen S. Involvement of metabotropic glutamate receptor 1, a G protein coupled receptor, in melanoma development. J Mol Med (Berl) 2004;82:735-49.
124. Matlaf LA, Harkins LE, Bezrookove V, Cobbs CS, Soroceanu L. Cytomegalovirus pp71 protein is expressed in human glioblastoma and promotes pro-angiogenic signaling by activation of stem cell factor. PLoS One 2013;8:e68176.
125. Matsukawa A, Kudo S, Maeda T, Numata K, Watanabe H, Takeda K, *et al.* Stat3 in resident macrophages as a repressor protein of inflammatory response. J Immunol 2005;175:3354-9.
126. Maussang D, Verzijl D, van Walsum M, Leurs R, Holl J, Pleskoff O, *et al.* Human cytomegalovirus-encoded chemokine receptor US28 promotes tumorigenesis. Proc Natl Acad Sci U S A 2006;103:13068-73.
127. McCarthy M, Auger D, Whittemore SR. Human cytomegalovirus causes productive infection and neuronal injury in differentiating fetal human central nervous system neuroepithelial precursor cells. J Hum Virol 2000;3:215-28.
128. McGivern DR, Lemon SM. Virus-specific mechanisms of carcinogenesis in hepatitis C virus associated liver cancer. Oncogene 2011;30:1969-83.
129. Mesri EA, Feitelson MA, Munger K. Human viral oncogenesis: A cancer hallmarks analysis. Cell Host Microbe 2014;15:266-82.
130. Michálek J, Horvath R. High incidence of Epstein-Barr virus, cytomegalovirus and human herpesvirus 6 infections in children with cancer. BMC Pediatr 2002;2:1.
131. Migone TS, Lin JX, Cereseto A, Mulloy JC, O'Shea JJ, Franchini G, *et al.* Constitutively activated jak-STAT pathway in T cells transformed with HTLV-I. Science 1995;269:79-81.
132. Mitchell DA, Xie W, Schmittling R, Learn C, Friedman A, McLendon RE, *et al.* Sensitive detection of human cytomegalovirus in tumors and peripheral blood of patients diagnosed with glioblastoma. Neuro Oncol 2008;10:10-8.
133. Mitchison TJ, Cramer LP. Actin-based cell motility and cell locomotion. Cell 1996;84:371-9.
134. Mocarski ES, Kemble GW, Lyle JM, Greaves RF. A deletion mutant in the human cytomegalovirus gene encoding IE1(491aa) is replication defective due to a failure in autoregulation. Proc Natl Acad Sci U S A 1996;93:11321-6.
135. Monick MM, Geist LJ, Stinski MF, Hunninghake GW. The immediate early genes of human cytomegalovirus upregulate expression of the cellular genes myc and fos. Am J Respir Cell Mol Biol 1992;7:251-6.
136. Munger J, Bajad SU, Coller HA, Shenk T, Rabinowitz JD. Dynamics of the cellular metabolome during human cytomegalovirus infection. PLoS Pathog 2006;2:e132.
137. Munger J, Bennett BD, Parikh A, Feng XJ, McArdle J, Rabitz HA, *et al.* Systems-level metabolic flux profiling identifies fatty acid synthesis as a target for antiviral therapy. Nat Biotechnol 2008;26:1179-86.
138. Muromoto R, Ikeda O, Okabe K, Togi S, Kamitani S, Fujimuro M, *et al.* Epstein-barr virus-derived EBNA2 regulates STAT3 activation. Biochem Biophys Res Commun 2009;378:439-43.
139. Naithani R, Huma LC, Holland LE, Shukla D, McCormick DL, Mehta RG, *et al.* Antiviral activity of phytochemicals: A comprehensive review. Mini Rev Med Chem 2008;8:1106-33.
140. Newsholme EA, Crabtree B, Ardawi MS. The role of high rates of glycolysis and glutamine utilization in rapidly dividing cells. Biosci Rep 1985;5:393-400.
141. Nicoletti F, Arcella A, Iacovelli L, Battaglia G, Giangaspero F, Melchiorri D, *et al.* Metabotropic glutamate receptors: New targets for the control of tumor growth? Trends Pharmacol Sci 2007;28:206-13.
142. Odeberg J, Wolmer N, Falci S, Westgren M, Seiger A, Söderberg-Nauclér C, *et al.* Human cytomegalovirus inhibits neuronal differentiation and induces apoptosis in human neural precursor cells. J Virol 2006;80:8929-39.
143. Ogura H, Murakami M, Okuyama Y, Tsuruoka M, Kitabayashi C, Kanamoto M, *et al.* Interleukin-17 promotes autoimmunity by triggering a positive-feedback loop via interleukin-6 induction. Immunity 2008;29:628-36.
144. Ogura T, Tanaka J, Kamiya S, Sato H, Ogura H, Hatano M, *et al.* Human cytomegalovirus persistent infection in a human central nervous system cell line: Production of a variant virus with different growth characteristics. J Gen Virol 1986;67 (Pt 12):2605-16.
145. Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells: Linking inflammation and cancer. J Immunol 2009;182:4499-506.
146. Park JS, Voitenko N, Petralia RS, Guan X, Xu JT, Steinberg JP, *et al.* Persistent inflammation induces gluR2 internalization via NMDA receptor-triggered PKC activation in dorsal horn neurons. J Neurosci 2009;29:3206-19.
147. Perlman JM, Argyle C. Lethal cytomegalovirus infection in preterm infants: Clinical, radiological, and neuropathological findings. Ann Neurol 1992;31:64-8.
148. Piao Y, Lu L, de Groot J. AMPA receptors promote perivascular glioma invasion via beta1 integrin-dependent adhesion to the extracellular matrix. Neuro Oncol 2009;11:260-73.
149. Pollock EJ, Todaro GJ. Radiation enhancement of SV40 transformation in 3T3 and human cells. Nature 1968;219:520-1.
150. Polster BM, Pevsner J, Hardwick JM. Viral bcl-2 homologs and their role in virus replication and associated diseases. Biochim Biophys Acta 2004;1644:211-27.
151. Poltermann S, Schlehofer B, Steindorf K, Schnitzler P, Geletneky K, Schlehofer JR, *et al.* Lack of association of herpesviruses with brain tumors. J Neurovirol 2006;12:90-9.
152. Porporato PE, Dhup S, Dadhich RK, Copetti T, Sonveaux P. Anticancer targets in the glycolytic metabolism of tumors: A comprehensive review. Front Pharmacol 2011;2:49.
153. Porporato PE, Filigheddu N, Pedro JM, Kroemer G, Galluzzi L. Mitochondrial metabolism and cancer. Cell Res 2018;28:265-80.
154. Presta M, Dell'Era P, Mitola S, Moroni E, Ronca R, Rusnati M, *et al.* Fibroblast growth factor/fibroblast growth factor receptor

system in angiogenesis. Cytokine Growth Factor Rev 2005;16:159-78.
155. Raftery MJ, Wieland D, Gronewald S, Kraus AA, Giese T, Schönrich G, *et al.* Shaping phenotype, function, and survival of dendritic cells by cytomegalovirus-encoded IL-10. J Immunol 2004;173:3383-91.
156. Ranganathan P, Clark PA, Kuo JS, Salamat MS, Kalejta RF. Significant association of multiple human cytomegalovirus genomic loci with glioblastoma multiforme samples. J Virol 2012;86:854-64.
157. Redpath S, Ghazal P, Gascoigne NR. Hijacking and exploitation of IL-10 by intracellular pathogens. Trends Microbiol 2001;9:86-92.
158. Reed JC. Dysregulation of apoptosis in cancer. J Clin Oncol 1999;17:2941-53.
159. Reeves MB, Compton T. Inhibition of inflammatory interleukin-6 activity via extracellular signal-regulated kinase-mitogen-activated protein kinase signaling antagonizes human cytomegalovirus reactivation from dendritic cells. J Virol 2011;85:12750-8.
160. Rivas C, Thlick AE, Parravicini C, Moore PS, Chang Y. Kaposi's sarcoma-associated herpesvirus LANA2 is a B-cell-specific latent viral protein that inhibits p53. J Virol 2001;75:429-38.
161. Rollins BJ. Inflammatory chemokines in cancer growth and progression. Eur J Cancer 2006;42:760-7.
162. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW, *et al.* Effect of daily aspirin on long-term risk of death due to cancer: Analysis of individual patient data from randomised trials. Lancet 2011;377:31-41.
163. Russo V, Martienssen RA, Riggs AD. Epigenic Mechanism of Gene Regulation. USA: Cold Spring Harbor Laboratory Press; 1996. p. 662.
164. Rzeski W, Ikonomidou C, Turski L. Glutamate antagonists limit tumor growth. Biochem Pharmacol 2002;64:1195-200.
165. Sadzuka Y, Sugiyama T, Shimoi K, Kinae N, Hirota S. Protective effect of flavonoids on doxorubicin-induced cardiotoxicity. Toxicol Lett 1997;92:1-7.
166. Sakao-Suzuki M, Kawasaki H, Akamatsu T, Meguro S, Miyajima H, Iwashita T, *et al.* Aberrant fetal macrophage/microglial reactions to cytomegalovirus infection. Ann Clin Transl Neurol 2014;1:570-88.
167. Samanta M, Harkins L, Klemm K, Britt WJ, Cobbs CS. High prevalence of human cytomegalovirus in prostatic intraepithelial neoplasia and prostatic carcinoma. J Urol 2003;170:998-1002.
168. Samavati L, Rastogi R, Du W, Hüttemann M, Fite A, Franchi L, *et al.* STAT3 tyrosine phosphorylation is critical for interleukin 1 beta and interleukin-6 production in response to lipopolysaccharide and live bacteria. Mol Immunol 2009;46:1867-77.
169. Sasaki K, Zhao X, Pardee AD, Ueda R, Fujita M, Sehra S, *et al.* Stat6 signaling suppresses VLA-4 expression by CD8+ T cells and limits their ability to infiltrate tumor lesions *in vivo*. J Immunol 2008;181:104-8.
170. Scheurer ME, Bondy ML, Aldape KD, Albrecht T, El-Zein R. Detection of human cytomegalovirus in different histological types of gliomas. Acta Neuropathol 2008;116:79-86.
171. Seleme MC, Kosmac K, Jonjic S, Britt WJ. Tumor necrosis factor alpha-induced recruitment of inflammatory mononuclear cells leads to inflammation and altered brain development in murine cytomegalovirus-infected newborn mice. J Virol 2017;91:e01983-16.
172. Semenza GL. HIF-1 and tumor progression: Pathophysiology and therapeutics. Trends Mol Med 2002;8:S62-7.
173. Seyfried TN, Flores RE, Poff AM, D'Agostino DP. Cancer as a metabolic disease: Implications for novel therapeutics. Carcinogenesis 2014;35:515-27.
174. Seyfried TN, Mukherjee P. Targeting energy metabolism in brain cancer: Review and hypothesis. Nutr Metab (Lond) 2005;2:30.
175. Seyfried TN, Shelton LM. Cancer as a metabolic disease. Nutr Metab (Lond) 2010;7:7.
176. Seyfried TN. Cancer as a Metabolic Disease: On the Origin, Management, and Prevention of Cancer. New York: John Wiley and Sons; 2012.
177. Shanmugam MK, Tergaonkar V, Seiti G. Role of inflammation in cancer development. Cancer Res 2005;65:5720-9.
178. Sharma MK, Seidlitz EP, Singh G. Cancer cells release glutamate via the cystine/glutamate antiporter. Biochem Biophys Res Commun 2010;391:91-5.
179. Sheng S, Qiao M, Pardee AB. Metastasis and AKT activation. J Cell Physiol 2009;218:451-4.
180. Sherry MM, Reeves A, Wu JK, Cochran BH. STAT3 is required for proliferation and maintenance of multipotency in glioblastoma stem cells. Stem Cells 2009;27:2383-92.
181. Silva EM, Mariano VS, Pastrez PR, Pinto MC, Castro AG, Syrjanen KJ, *et al.* High systemic IL-6 is associated with worse prognosis in patients with non-small cell lung cancer. PLoS One 2017;12:e0181125.
182. Sinclair J, Sissons P. Latency and reactivation of human cytomegalovirus. J Gen Virol 2006;87:1763-79.
183. Slinger E, Maussang D, Schreiber A, Siderius M, Rahbar A, Fraile-Ramos A, *et al.* HCMV-encoded chemokine receptor US28 mediates proliferative signaling through the IL-6-STAT3 axis. Sci Signal 2010;3:ra58.
184. Söderberg-Nauclér C, Johnsen JI. Cytomegalovirus in human brain tumors: Role in pathogenesis and potential treatment options. World J Exp Med 2015;5:1-10.
185. Söderberg-Nauclér C. Does cytomegalovirus play a causative role in the development of various inflammatory diseases and cancer? J Intern Med 2006;259:219-46.
186. Söderberg-Nauclér C. HCMV microinfections in inflammatory diseases and cancer. J Clin Virol 2008;41:218-23.
187. Song G, Ouyang G, Bao S. The activation of akt/PKB signaling pathway and cell survival. J Cell Mol Med 2005;9:59-71.
188. Sontheimer H. A role for glutamate in growth and invasion of primary brain tumors. J Neurochem 2008;105:287-95.
189. Soroceanu L, Akhavan A, Cobbs CS. Platelet-derived growth factor-alpha receptor activation is required for human cytomegalovirus infection. Nature 2008;455:391-5.
190. Soroceanu L, Cobbs CS. Is HCMV a tumor promoter? Virus Res 2011;157:193-203.
191. Soroceanu L, Matlaf L, Bezrookove V, Harkins L, Martinez R, Greene M, *et al.* Human cytomegalovirus US28 found in glioblastoma promotes an invasive and angiogenic phenotype. Cancer Res 2011;71:6643-53.

192. Soroceanu L, Matlaf L, Khan S, Akhavan A, Singer E, Bezrookove V, *et al.* Cytomegalovirus immediate-early proteins promote stemness properties in glioblastoma. Cancer Res 2015;75:3065-76.
193. Speir E, Yu ZX, Ferrans VJ, Huang ES, Epstein SE. Aspirin attenuates cytomegalovirus infectivity and gene expression mediated by cyclooxygenase-2 in coronary artery smooth muscle cells. Circ Res 1998;83:210-6.
194. Spencer JP, Vafeiadou K, Williams RJ, Vauzour D. Neuroinflammation: Modulation by flavonoids and mechanisms of action. Mol Aspects Med 2012;33:83-97.
195. Spencer JV, Lockridge KM, Barry PA, Lin G, Tsang M, Penfold ME, *et al.* Potent immunosuppressive activities of cytomegalovirus-encoded interleukin-10. J Virol 2002;76:1285-92.
196. Stangherlin LM, Castro FL, Medeiros RS, Guerra JM, Kimura LM, Shirata NK, *et al.* Human cytomegalovirus DNA quantification and gene expression in gliomas of different grades. PLoS One 2016;11:e0159604.
197. Steck TL, Kaufman S, Bader JP. Glycolysis in chick embryo cell cultures transformed by rous sarcoma virus. Cancer Res 1968;28:1611-9.
198. Stepulak A, Sifringer M, Rzeski W, Endesfelder S, Gratopp A, Pohl EE, *et al.* NMDA antagonist inhibits the extracellular signal-regulated kinase pathway and suppresses cancer growth. Proc Natl Acad Sci U S A 2005;102:15605-10.
199. Stöppler H, Malerczyk C, Block K, Aigner A, Czubayko F. The human papillomavirus (HPV) 16 E6 oncoprotein leads to an increase in gene expression of the angiogenic switch molecule FGF-BP in non-immortalized human keratinocytes. Oncogene 2001;20:7430-6.
200. Stråât K, Liu C, Rahbar A, Zhu Q, Liu L, Wolmer-Solberg N, *et al.* Activation of telomerase by human cytomegalovirus. J Natl Cancer Inst 2009;101:488-97.
201. Studer E, Bertoni G, Candrian U. Detection and characterization of pestivirus contaminations in human live viral vaccines. Biologicals 2002;30:289-96.
202. Suh Y, Afaq F, Johnson JJ, Mukhtar H. A plant flavonoid fisetin induces apoptosis in colon cancer cells by inhibition of COX2 and wnt/EGFR/NF-kappaB-signaling pathways. Carcinogenesis 2009;30:300-7.
203. Sumimoto H, Imabayashi F, Iwata T, Kawakami Y. The BRAF-MAPK signaling pathway is essential for cancer-immune evasion in human melanoma cells. J Exp Med 2006;203:1651-6.
204. Sun S, Steinberg BM. PTEN is a negative regulator of STAT3 activation in human papillomavirus-infected cells. J Gen Virol 2002;83:1651-8.
205. Taher C, de Boniface J, Mohammad AA, Religa P, Hartman J, Yaiw KC, *et al.* High prevalence of human cytomegalovirus proteins and nucleic acids in primary breast cancer and metastatic sentinel lymph nodes. PLoS One 2013;8:e56795.
206. Takano T, Lin JH, Arcuino G, Gao Q, Yang J, Nedergaard M, *et al.* Glutamate release promotes growth of malignant gliomas. Nat Med 2001;7:1010-5.
207. Takeda K, Akira S. STAT family of transcription factors in cytokine-mediated biological responses. Cytokine Growth Factor Rev 2000;11:199-207.
208. Tan WF, Lin LP, Li MH, Zhang YX, Tong YG, Xiao D, *et al.* Quercetin, a dietary-derived flavonoid, possesses antiangiogenic potential. Eur J Pharmacol 2003;459:255-62.
209. Tanaka J, Ogura T, Iida H, Sato H, Hatano M. Inhibitors of prostaglandin synthesis inhibit growth of human cytomegalovirus and reactivation of latent virus in a productively and latently infected human cell line. Virology 1988;163:205-8.
210. Tang FY, Chen CY, Shyu HW, Hong S, Chen HM, Chiou YH, *et al.* Resveratrol induces cell death and inhibits human herpesvirus 8 replication in primary effusion lymphoma cells. Chem Biol Interact 2015;242:372-9.
211. Victoria JG, Wang C, Jones MS, Jaing C, McLoughlin K, Gardner S, *et al.* Viral nucleic acids in live-attenuated vaccines: Detection of minority variants and an adventitious virus. J Virol 2010;84:6033-40.
212. Vinay DS, Ryan EP, Pawelec G, Talib WH, Stagg J, Elkord E, *et al.* Immune evasion in cancer: Mechanistic basis and therapeutic strategies. Semin Cancer Biol 2015;35 Suppl:S185-98.
213. Wang D, Dubois RN. Eicosanoids and cancer. Nat Rev Cancer 2010;10:181-93.
214. Wang HW, Sharp TV, Koumi A, Koentges G, Boshoff C. Characterization of an anti-apoptotic glycoprotein encoded by kaposi's sarcoma-associated herpesvirus which resembles a spliced variant of human survivin. EMBO J 2002;21:2602-15.
215. Wang L, Liu PB, Hong JS. Inhibition of microglial activation by the herbal flavonoid baicalein attenuates inflammation-mediated degeneration of dopaminergic neurons. J Neural Transm 2005;112:331-47.
216. Wang L, Yi T, Kortylewski M, Pardoll DM, Zeng D, Yu H, *et al.* IL-17 can promote tumor growth through an IL-6-stat3 signaling pathway. J Exp Med 2009;206:1457-64.
217. Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. J Gen Physiol 1927;8:519-30.
218. Williamson CD, Colberg-Poley AM. Intracellular sorting signals for sequential trafficking of human cytomegalovirus UL37 proteins to the endoplasmic reticulum and mitochondria. J Virol 2010;84:6400-9.
219. Williamson CD, DeBiasi RL, Colberg-Poley AM. Viral product trafficking to mitochondria, mechanisms and roles in pathogenesis. Infect Disord Drug Targets 2012;12:18-37.
220. Wilson M, Gill SK, MacPherson L, English M, Arvanitis TN, Peet AC, *et al.* Noninvasive detection of glutamate predicts survival in pediatric medulloblastoma. Clin Cancer Res 2014;20:4532-9.
221. Winland CD, Welsh N, Sepulveda-Rodriguez A, Vicini S, Maguire-Zeiss KA. Inflammation alters AMPA-stimulated calcium responses in dorsal striatal D2 but not D1 spiny projection neurons. Eur J Neurosci 2017;46:2519-33.
222. Wise DR, DeBerardinis RJ, Mancuso A, Sayed N, Zhang XY, Pfeiffer HK, *et al.* Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. Proc Natl Acad Sci U S A 2008;105:18782-7.
223. Wu CC, Fang CY, Hsu HY, Chen YJ, Chou SP, Huang SY, *et al.* Luteolin inhibits epstein-barr virus lytic reactivation by repressing the promoter activities of immediate-early genes. Antiviral Res 2016;132:99-110.
224. Yan Y, Liu F, Han L, Zhao L, Chen J, Olopade OI, *et al.* HIF-

2α promotes conversion to a stem cell phenotype and induces chemoresistance in breast cancer cells by activating wnt and notch pathways. J Exp Clin Cancer Res 2018;37:256.
225. Yang C, Sudderth J, Dang T, Bachoo RM, McDonald JG, DeBerardinis RJ, *et al*. Glioblastoma cells require glutamate dehydrogenase to survive impairments of glucose metabolism or akt signaling. Cancer Res 2009;69:7986-93.
226. Ye ZC, Sontheimer H. Glioma cells release excitotoxic concentrations of glutamate. Cancer Res 1999;59:4383-91.
227. Yu H, Jove R. The STATs of cancer--new molecular targets come of age. Nat Rev Cancer 2004;4:97-105.
228. Yu H, Kortylewski M, Pardoll D. Crosstalk between cancer and immune cells: Role of STAT3 in the tumour microenvironment. Nat Rev Immunol 2007;7:41-51.
229. Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: A leading role for STAT3. Nat Rev Cancer 2009;9:798-809.
230. Yu Y, Maguire TG, Alwine JC. Human cytomegalovirus activates glucose transporter 4 expression to increase glucose uptake during infection. J Virol 2011;85:1573-80.
231. Yuneva M, Zamboni N, Oefner P, Sachidanandam R, Lazebnik Y. Deficiency in glutamine but not glucose induces MYC-dependent apoptosis in human cells. J Cell Biol 2007;178:93-105.
232. Yurochko AD, Kowalik TF, Huong SM, Huang ES. Human cytomegalovirus upregulates NF-kappa B activity by transactivating the NF-kappa B p105/p50 and p65 promoters. J Virol 1995;69:5391-400.
233. Zhang HG, Grizzle WE. Exosomes and cancer: A newly described pathway of immune suppression. Clin Cancer Res 2011;17:959-64.
234. Zur Hausen H. The search for infectious causes of human cancers: Where and why. Virology 2009;392:1-10.

How to cite this article: Blaylock RL. Accelerated cancer aggressiveness by viral oncomodulation: New targets and newer natural treatments for cancer control and treatment. Surg Neurol Int 2019;10:199.