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Advances in Tumor Virology

Chronic Inflammation in Cancer: The Role of Human Viruses

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ABSTRACT: While the process of inflammation is a normal biological process to protect the body from harmful stimuli, chronic inflammation has been linked to a number of human diseases, including cancer. A number of agents can stimulate a chronic inflammatory response, which in turn promotes carcinogenesis. Here, we will describe how chronic inflammation is established through changes in cytokine signaling, perturbations of the NF-κB pathway, DNA damage, and physiological changes within the microenvironment and how these changes also contribute to tumorigenesis. In addition, we will describe the direct and indirect mechanisms by which infection by six viruses—Epstein-Barr, human herpesvirus-8, hepatitis B and C, human papilloma, and human T-lymphotropic virus type 1—induces chronic inflammation leading to tumor formation.

KEYWORDS: chronic inflammation, viruses, cancer, cytokines

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Introduction

Cancer is a heterogeneous group of disorders characterized by uncontrolled cellular proliferation, invasion into surrounding tissues, and metastatic spread to secondary sites. Cancer can occur in virtually every organ site in the body, and over 100 different types of cancer have been described. In 2012, 14.1 million people were diagnosed with and 8.2 million people died from cancer worldwide.[1] The incidence of cancer is expected to increase 53% to 21.6 million people by 2030.[2] Worldwide, chronic inflammation and/or chronic infection are associated with 25% of all human cancers.[3]

The idea that chronic inflammation is associated with carcinogenesis is not new—nearly 2,000 years ago, Greek physician Galenus proposed that, based on physical similarities, tumors may evolve from inflammatory lesions.[4] In 1863, Virchow identified leukocytes in areas of neoplasia, furthering the relationship between inflammation and cancer.[5] More recently, tumors have been described as "wounds that do not heal" based on physiological similarities between tumors and inflammation,[6] including recruitment of immune response cells to the tumor and release of inflammatory mediators, resulting in increased cellular proliferation and angiogenesis and decreased apoptosis and immune surveillance.[7] Conditions involving chronic inflammation have been associated with a number of tumor types. Risk of esophageal cancer is 50–100 times higher in patients with chronic acid reflux disease compared to those without, while exposure to asbestos increases the risk of mesothelioma in a dose-dependent manner.

Infectious agents have also been associated with increased risk of certain types of tumors, accounting for about two million cancer cases each year.[8] For example, infection by the bacterium *Helicobacter pylori* (*H. pylori*) causes chronic

Table 1. Six viruses associated with tumor formation via chronic inflammation.

ONCOVIRUS	TYPE OF VIRUS	PRIMARY ROUTE OF TRANSMISSION	ASSOCIATED CANCERS
EBV	dsDNA	Saliva/Upper respiratory secretions	Burkitt's lymphoma (BL), nasopharyngeal carcinoma (NPC), Hodgkin lymphoma (HL), gastric carcinomas (GC), and other lymphomas
HHV8	dsDNA	Sexual/Organ transplantation	Kaposi's sarcoma (KS), Primary effusion lymphoma (PEL)
HBV	dsDNA	Sexual/Perinatal/Blood	Hepatocellular carcinoma (HCC)
HCV	ssRNA	Blood/Sexual	Hepatocellular carcinoma (HCC)
HPV	dsDNA	Sexual and casual contact	Cervical, anal, genital, and various head and neck cancers
HTLV-1	ssRNA-RT	Sexual/Vertical through breastfeeding	Adult T-cell leukemia and lymphoma (ATLL)

inflammation and increases the risk of developing gastric cancer.[9] In addition, six viruses have been classified as carcinogenic by the International Agency for Research on Cancer (IARC) (Table 1). Each of the viruses may increase the risk of tumor development by eliciting an immune response, resulting in a chronically inflamed microenvironment (Fig. 1). In this manuscript, we detail the mechanisms by which chronic inflammation stimulates carcinogenesis, and then describe how Epstein-Barr virus (EBV), human herpesvirus-8 (HHV8), hepatitis B (HBV), hepatitis C (HCV), human papilloma virus (HPV), and human T-cell lymphotropic virus type 1 (HTLV-1) contribute to tumorigenesis through chronic inflammation.

Physiology of Chronic Inflammation

Inflammation is the body's primary mode of protecting itself from harmful stimuli, such as irritants, damaged or dead cells, or pathogens, and is involved in maintaining homeostasis.[10] The inflammatory response is mediated by a number of proteins, including chemokines, which control the activation and accumulation of leukocytes. Normally, once the threat of infection has passed and the tissue is repaired, the inflammatory response begins its resolution pathway; however, failure to resolve this response can lead to chronic inflammation and a number of detrimental downstream effects. For example, lymphocytes recruited to the affected tissue may, in an attempt to eliminate pathogens, activate macrophages. These may then attack body's own cells, causing significant damage.[11] Oxidative stress (OS), which is the primary cause of DNA damage, apoptosis, and neoplastic transformation, activates a number of transcription factors, which then lead to generation of additional reactive oxygen species (ROS), further increasing cellular stress levels.[12]

Chronic inflammation can influence all stages of tumorigenesis, either directly or indirectly. DNA damage in response to inflammation may catalyze the earliest steps in tumor development. Physiologic changes in cells of the stromal compartment may promote tumor progression by creating an immunotolerant microenvironment, and increased expression of cytokines may promote cellular proliferation and metastasis. In addition, dysregulation of the NF-κB pathway by inflammation can affect cellular mechanisms such as apoptosis and cell growth.

Cytokines. Cytokines are pivotal in regulating host defense systems via normal and abnormal homeostatic mechanisms. Cytokines are polypeptide mediators and resemble hormones in their structure and function. Certain cytokines are responsible for triggering acute inflammation while others cause humoral response of chronic inflammation and yet another set mediates cellular responses.[13] The cytokine family can be divided into four primary subgroups: chemokines, interferons, interleukins, and tumor necrosis factors (Table 2).

DNA damage. Chronic inflammatory conditions generate ROS and reactive nitrogen species (RNS) leading to oxidative and nitrative stress and DNA damage. If errors are not properly repaired, consequent DNA lesions have tumorigenic potential through aberrant expression of oncogenes and tumor suppressor genes.[14] Excessive amounts of ROS and RNS, and lowered concentration of or decreased effectiveness of antioxidant defenses can damage DNA, or alter nuclear and cytoplasmic signal transduction pathways that control the expression of stress-induced genes and proteins. Both processes can regulate cell differentiation, proliferation, and apoptosis, and alteration of these processes can contribute to carcinogenesis. This damage or mutation to DNA is capable of triggering carcinogenesis and resulting in cancer through activation of specific transcription factors, such as NF-κB.[15]

Dysregulation of the NF-κB pathway. NF-κB is a transcription factor responsible for controlling the expression of inflammatory response through regulation of cytokines. As such, the dysregulation of NF-κB can have significant side effects. Perturbation of the NF-κB pathway, which is controlled by cytokines such as IL-1β and TNF-α,[16] is associated with increased levels of OS and ROS, resulting in damage to DNA[17] and carcinogenesis. In addition to DNA damage, dysregulation of the NF-κB pathway has also been associated with increased basal inflammation,[18] irregular immune system development, autoimmune diseases, septic shock, and even viral infection.[19]

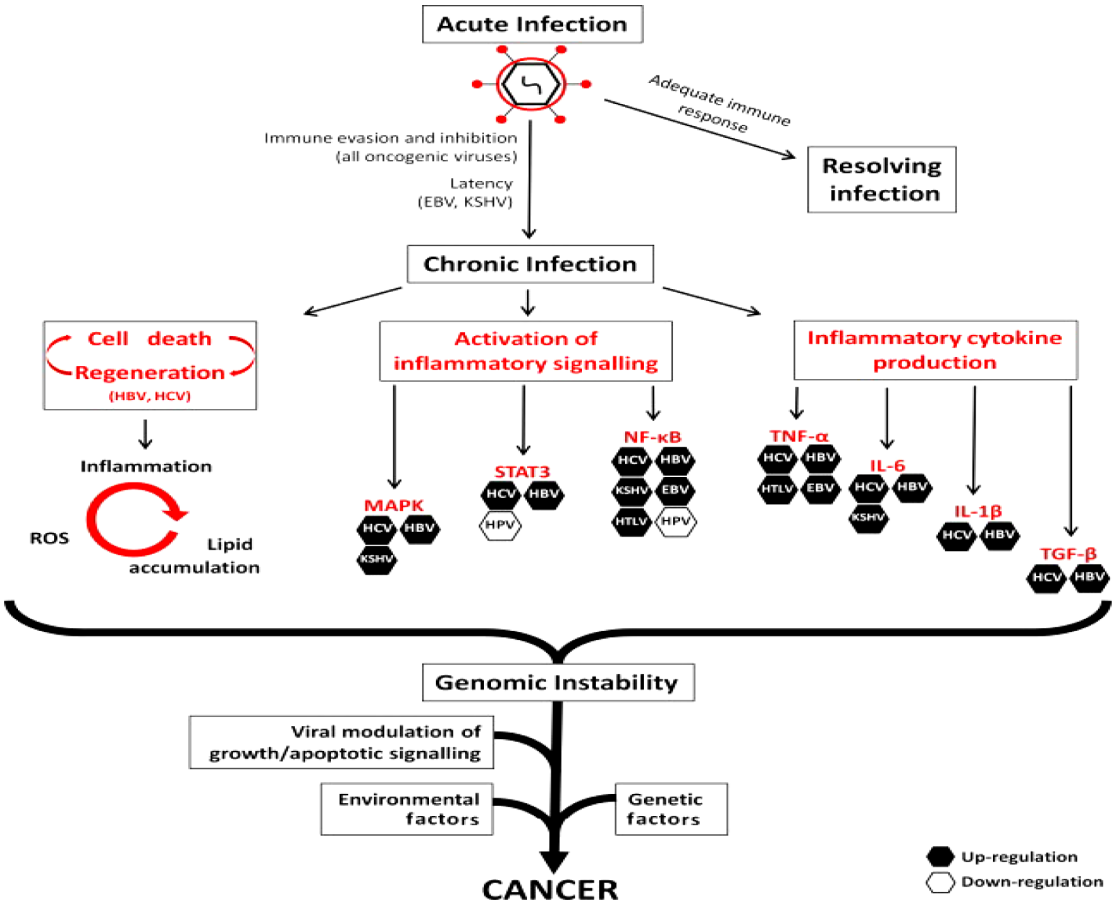

Figure 1. Inflammation resulting from chronic viral infection contributes to cancer development. Following infection, oncogenic viruses utilize a number of mechanisms to evade the host immune system, occasionally resulting in chronic infection. Chronic activation of inflammatory signaling can result, mediated directly by the virus or indirectly as a result of viral propagation. Direct activation of inflammation is generally mediated by viral proteins capable of activating inflammatory signaling cascades and/or host inflammatory cytokines. Conversely, some oncogenic viruses possess viral homologs of human inflammatory cytokines including vIL-6 (KSHV) and vIL-10 (EBV). The hepatotrophic viruses HBV and HCV, especially, induce significant indirect inflammation as a result of viral replication-induced ROS, lipid accumulation, and immune recognition. As a result, a substantial amount of cell death and resulting hepatocyte regeneration occurs that contributes to cancer progression.

NF-κB activation can occur through two different pathways—canonical and non-canonical. The NF-κB canonical pathway is activated by toll-like receptors (TLRs) and proinflammatory cytokines, mainly TNF-α and IL-1,[17] while the non-canonical pathway is initially activated by TNF-family cytokines. Activation of the NF-κB pathway results in the transcriptional activation of over 400 different genes that play a pivotal role in the inflammatory process and carcinogenesis. For example, NF-κB can act as an inhibitor of pathogen-induced apoptosis in macrophages,[20] allowing potentially cancerous cells to avoid apoptosis and continue replicating. In addition, activation of the NF-κB pathway alters the expression of genes responsible for inflammation, immunoregulation, tumor cell proliferation, invasion, metastasis, angiogenesis, chemoresistance, and radioresistance.[21]

Physiological changes to stromal cells. Numerous studies have demonstrated that the tumor microenvironment is intimately involved in the promotion of tumor growth and metastasis. Components of the stroma, including tumor associated macrophages (TAMs), T cells, and cancer-associated fibroblasts (CAFs), contribute to chronic inflammation and tumorigenesis. For example, TAMs are recruited to tumor stromal cells by chemokines such as CCL2, CCL5, and CXCL1. Once recruited, TAMs produce additional CCL2 in order to recruit additional TAMs,[22] thus extending the lifespan of tumor cells by diverting the natural immune response via the production of immunosuppressive cytokines, such as IL-10 and TGF-β.[23] In addition, TAMs have been associated with defective NF-κB activation, further impairing immune response.[24] T cells also play a unique role in the normal immune response and development and proliferation of cancer. Helper T cells (Th) are instrumental in regulating the entire immune system, including cytotoxic T cells, B-cell responses, and innate immunity.[25] The proinflammatory response associated with Th cells, however, can be overridden by the anti-inflammatory properties of Tregs, which maintain tolerance to self-antigens, preventing autoimmunity when the immune system fails to discriminate between its own cells

Table 2. Cytokines involved in chronic inflammation and tumorigenesis.

CYTOKINES	SOURCE	TARGETS
Chemokines	Macrophages, endothelia, fibroblasts, epithelia	Increased phagocyte, B- and, T-lymphocyte migration, wound repair
Interferons		
IFN-1 α	Macrophages	Increased activation of NK lymphocytes, viral immunity, MHC class I
IFN-1 β	Fibroblasts	Increased activation of NK lymphocytes, viral immunity, MHC class I
IFN-γ	Th1, Tc and NK lymphocytes	Increased B-lymphocyte subtype switch, Th1-lymphocytes differentiation, macrophage activation, antigen processing and MHC class I
Interleukins		
IL-1	Macrophages, endothelia, epithelia	Increased inflammation, endothelial cells and expression of acute phase proteins in hepatocytes
IL-2	T-lymphocytes	Increased survival, proliferation and cytokine production of T-lymphocytes, cytokine and antibody production of T-lymphocytes and proliferation and activation of NK-lymphocytes
IL-4	Th2-lymphocytes	Increased isotope switch of B-lymphocytes, proliferation and differentiation of Th2-lymphocytes, proliferation of mast cells and decreased IFN-IIγ response of macrophages
IL-5	Th2-lymphocytes	Increased proliferation and isotope switch of B-lymphocytes and proliferation and activation of eosinophils
IL-6	Macrophages, endothelial and T-lymphocytes	Increased B-lymphocyte proliferation and expression of acute phase proteins in hepatocytes
IL-10	Macrophages and T-lymphocytes	Decreased expression of IL-12 in macrophage and dendritic cells
IL-12	Macrophages and dendritic cells	Increased differentiation of Th1-lymphocytes, expression of IFNII-γ in Tc- and NK-lymphocytes
IL-13	Th2- and NK-lymphocytes, mast cells	Increased B-lymphocyte isotope switch and macrophage collagen expression
IL-15	Macrophages	Increased proliferation of NK- and T-lymphocytes
IL-17	T-lymphocytes	Increased expression of cytokines, chemokines, growth factors
IL-18	Macrophages	Increased IFNII-γ expression in NK- and T-lymphocytes
IL-23	Macrophages and dendritic cells	Increased expression of IL-17 in T-lymphocytes
IL-27	Macrophages and dendritic cells	Increased IFNII-γ expression in NK-lymphocytes, inhibition and/or differentiation of Th1-lymphocytes
Tumor necrosis factors		
Lymphotoxins	T-lymphocytes	Increased B- and T-lymphocyte development, neutrophil migration and activation
TNF	Macrophages and T-lymphocytes	Increased inflammation, endothelial cells, expression of acute phase proteins in hepatocytes and activation of neutrophils

Note: Adapted from *The Immune Network* http://nfs.unipv.it/nfs/minf/dispense/immunology/lectures/files/immune_network.html

and foreign cells. In many types of human solid tumors, Tregs accumulate and act to promote tumor escape from cytotoxic immune responses.[26] Finally, CAFs may alter the inflammatory status of the tumor microenvironment as they express proinflammatory gene signatures, including genes such as cyclooxygenase (COX-2), CXCL1, IL-1β, IL-6, TFN-α, and numerous others.[27–30] CAFs also modulate inflammation by skewing the balance between tumor-promoting (Th2, Th17, and Tregs) and tumor-suppressing (Th1) lymphocytes.[31] Thus, the balance of CAFs, T cells, and TAMs can promote a pro-tumorigenic inflammatory microenvironment.

Viral Infection, Chronic Inflammation, and Cancer

Viruses are infectious agents that require an outside host to replicate and exert their effects. Viruses can spread through various transmission routes (airborne, foodborne, waterborne, vector borne), making them very difficult to control and combat; for example, the Spanish Flu infected approximately 500 million people or 1/3 of the world's population at that time.[32] In addition to human devastation, viruses can have significant economic impacts; it is estimated that in 2003, the economic burden to the USA caused by noncervical HPV was approximately $418 million.[33] Oncoviruses have been known to cause cancer for many years, and recent research indicates that viruses affect cancer progression and development directly or indirectly. Viral proteins can directly stimulate cell growth and proliferation, obstruct apoptosis, and/or inhibit immune cell recognition. Additionally, viruses are also able to alter pathways involved in inflammation-related processes, thereby indirectly increasing carcinogenesis. To date, six viruses have

been classified as type 1 carcinogens by the IARC, and the mechanisms by which each promotes tumorigenesis through chronic inflammation are described in detail below.

Epstein-Barr virus. The EBV is a double-stranded DNA virus of the *Herpesviridae* family. EBV, which infects ~95% of the world's population, was the first virus to be shown to definitively cause cancer in humans.[34] In under-developed countries, infection with EBV occurs early in life and usually does not produce symptoms, while in developed countries, infection with EBV is more likely to occur in adolescence or adulthood, where it may result in infectious mononucleosis. Route of infection is through the oropharynx, where primary EBV infection has a lytic component generating new virions. Once an immune response is mounted against the virus, it exists as a latent infection within B cells. Expression of a subset of genes, including six nuclear antigens, three latent membrane proteins, and two abundantly expressed RNAs allow EBV to evade immune surveillance, and once infected, patients remain carriers for life.[35,36]

In 1958, frequent diagnosis of Burkitt's lymphoma (BL) in children from regions of equatorial Africa led to the hypothesis that a viral vector may be causing this cancer; in 1964, EBV was identified as the causative agent.[37] EBV has since been associated with other cancers including Hodgkin lymphoma, undifferentiated nasopharyngeal carcinoma (NPC), T-cell lymphoma, and gastric cancer.[38] The disparate sequelae in patients infected with EBV—the majority of whom never develop tumors—may be attributable to environmental and geographic factors; for example, co-infection with malaria may increase the risk of developing BL in Central Africa while dietary factors in China may influence the risk of NPC. Recent data suggest that different EBV strains may account for different tumor types.[39] In 1997, the IARC classified EBV as a Class I carcinogen deeming it carcinogenic to humans.[40]

EBV may influence tumorigenesis indirectly by promoting chronic inflammation. Expression of latent membrane protein 1 (LMP1) within infected B cells has been shown to activate various inflammatory cytokines leading to perturbations in pro-tumorigenic pathways such as the NF-κB pathway.[41] In a transgenic mouse model, expression of LMP1 upregulated proinflammatory cytokines and chemokines that activate the NF-κB pathway as well as STAT3, a key regulator of inflammation.[42] Growth of T/NK lymphoma cells is dependent upon release of cytokines from a T cell-rich microenvironment; latent EBV establishes a proinflammatory microenvironment in T cells as LMP1 activates the NF-κB pathway, resulting in the expression of TNF-α, IFN-γ, and IL-1β cytokines.[43] Finally, in patients with EBV-positive gastric cancer, increased levels of the EBV lytic proteins were associated with severe grade chronic inflammation, suggesting that in the gastric microenvironment, reactivation of EBV to a lytic stage promotes inflammation.[44]

The importance of NF-κB signaling, a critical inflammatory pathway, in cancer development is well documented in EBV-associated malignancies. Aberrant activation of distinct NF-κB signals has been detected in EBV-positive NPCs; inhibition of this pathway effectively suppressed the growth of EBV-positive cells in vitro.[45] Of note, gene expression analysis revealed that NF-κB signaling regulates multiple chemokines and their receptors, which in turn may cause the influx of tumor infiltrating lymphocytes, a common characteristic of NPC.[46]

EBV may also promote tumor initiation and progression through the induction of inflammatory cytokines. For example, infection of peripheral blood mononuclear cells by EBV can enhance expression of IL-1 and IL-6 while inhibiting expression of TNF-α.[47] Recent data demonstrate that IL-6R, the cognate receptor for IL-6, is expressed at high levels in nasopharyngeal epithelial cell membranes, while IL-6 is expressed at high levels in the inflammatory stromal microenvironment of NPC. Binding of IL-6 to IL-6R subsequently activates STAT3, leading to tumor initiation, growth, and survival.[48] Furthermore, IL-6 mediated STAT3 activation may induce the production of inducible nitric oxide synthase (iNOS) in NPC resulting in mutagenic DNA lesions.[49] Immunofluorescent staining of EBV-positive NPC tissue samples revealed strong iNOS expression and DNA lesions in cancer cells and stromal inflammatory cells of NPC patients. Similar staining patterns were seen in EBV-positive patients with chronic nasopharyngitis although the intensities were significantly weaker, and little to no expression was detected in EBV-negative subjects.[49] Together, these data demonstrate that lifelong presence of EBV in infected individuals, even in a latent state, contributes to a highly inflammatory microenvironment, favorable for the initiation and promotion of tumors.

Human herpesvirus 8 (Kaposi's sarcoma associated herpesvirus). Like EBV, HHV8 is a large dsDNA oncovirus belonging to the *Herpesviridae* family. HHV8 was discovered in 1994. The virus is primarily transmitted through sexual contact but can also occur from organ donation. In developing countries, transmission is also believed to occur through casual, non-sexual contact.[40] HHV8 infection is uncommon in North America and northern Europe with infection rates ≤10%; higher rates are seen in Mediterranean countries, while ~50% of people in sub-Saharan Africa are infected.[50] HHV8 causes Kaposi's sarcoma (KS), a cancer of the blood vessels common in those who are immunocompromised, particularly AIDS patients. It is also the causative agent of primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD), a lymphoproliferative disorder similar to lymphoma. As with EBV, pathogenicity of HHV8 depends on other cofactors, including co-infection with HIV or an immunocompromised host background.[51]

As with EBV, the ability of HHV8 to evade immune surveillance allows it to persist lifelong in a latent state where it can cause low-grade chronic inflammation in the host. HHV8-infected cells and infiltrating inflammatory cells serve as sources for the numerous growth factors and cytokines

required to support the development of KS. HHV8 can act within infected endothelial cells to induce transcription of Ang-2, present in KS tumors at high levels.[52] Reactivation of HHV8 to a lytic stage can be stimulated by the inflammatory marker protein MAP4K4, leading to increased expression of COX-2. Elevated COX-2 levels have been detected in KS tissue samples, and high expression of COX-2 in HHV8-infected cell lines elicited secretion of various inflammatory cytokines, growth factors, and angiogenic factors while inhibition of COX-2 significantly diminished their expression and contribution in creating a KS lesion-like microenvironment.[53] When reactivated to a lytic stage, HHV8 can further promote an inflammatory response through the expression of the viral cytokine vIL-6,[54] facilitating tumor development.

Modulation of the NF-κB signaling pathway by HHV8 leads to an inflammatory environment[55] and allows the virus to evade immune recognition and persist in a latent state. This constitutive activation of NF-κB results in increased proliferation and survival of infected cells leading to genetic instability and accumulation of genetic alterations and therefore a greater likelihood of cancer.[56] Studies in both KS and PEL cells demonstrated that infection by HHV8 activates an IFI16-dependent inflammasome that creates a constant innate immune response against the latent HHV8 genome, leading to chronic inflammation.[57] Expression of the HHV8-encoded latent protein vFLIP K13 upregulates the expression of a number of NF-κB responsive genes involved in cytokine signaling, cell death, adhesion, inflammation, and immune response characteristics of PEL.[58]

Hepatitis B virus. HBV, a member of the *Hepadnaviridae* family, is a small DNA virus with a circular genome composed of single- and double-stranded DNA. The most common modes of HBV transmission are through exposure to contaminated blood sources, from mother to child during childbirth, or through sexual or other forms of intimate contact. Acute infection typically resolves spontaneously; however, in newborns and small children, infection can become chronic. It is estimated that one-third of the world's population has been infected with HBV at some point in their lives including 350 million people who are chronically infected (http://www.who.int/whosis/whostat/EN_WHS09_Full.pdf?ua=1). Chronic HBV infection is the most significant risk factor for development of hepatocellular carcinoma (HCC), with higher incidence in parts of the world where HBV infections are endemic. Up to 60% of HCC cases in Africa and East Asia are attributable to widespread HBV infection, compared to 20% of cases in Europe and the United States.[59] Patients with chronic viral hepatitis have 100-fold elevated relative risk for development of HCC.[60] HBV is non-cytopathic and causes minimal to no damage to the hepatocyte; rather, HBV-mediated liver damage is largely attributable to sustained inflammatory conditions stimulated by the virus. Chronic viral hepatitis is characterized by persistent inflammation, liver cell destruction, and regeneration through immune-mediated mechanisms. An inefficient and weak cytotoxic T cell response (CTL), incapable of clearing HBV from the liver, promotes this continuous cycle of cell death and subsequent regeneration resulting in cirrhosis and HCC.[61] In a HBV-transgenic mouse model, despite the absence of viral integration and transactivation, HCC developed, suggesting that liver damage was caused by CTL-mediated destruction of infected hepatocytes rather than by the virus itself.[62] Abnormal DNA methylation patterns are frequently detected in tumor cells associated with chronic inflammation.[63] Mice infected with HBV or HCV had an activated NK response and significantly increased IFN-γ expression and OS in the liver tissue. This NK-mediated response correlated with the induction of DNA methylation contributing to HCC-associated inflammation. Inhibition of NK activity reduced IFN-γ levels providing compelling evidence that NK cell function and the resulting inflammatory mechanisms are essential for aberrant DNA methylation, which may promote HCC.[64]

The chronic inflammatory processes that induce OS and increase production of ROS have been detected in patients with viral hepatitis where they activate numerous cytokines and growth factors, which in turn can contribute to the further production of reactive species.[65] This persistent hepatic OS also causes progressive accumulation of DNA damage in the liver resulting in tissue damage. For example, ethenodeoxyadenosine, a DNA adduct with mutagenic potential, has been detected at extremely high levels in the urine of HBV patients with chronic hepatitis and liver cirrhosis, and its formation is likely a result of HBV-induced chronic inflammatory processes.[66] Additionally, increased levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a DNA lesion produced by hydroxyl radicals, a marker of OS and a cancer risk factor, have been found in patients with chronic viral hepatitis.[67] Although the presence of these oxidative markers is unfavorable, use of these biomarkers clinically to monitor disease progression is not yet possible.

Hepatitis C virus. HCV is a small single-stranded RNA virus belonging to the *Flaviviridae* family. HCV is a blood borne virus most commonly transmitted through exposures to infected blood such as injection drug use, donated blood and blood products, needlesticks, or vertical transmission from mother to child. HCV is less commonly spread through sexual contact and by sharing personal care items.[68] Worldwide, ~170 million people are living with chronic hepatitis C. HCV infection is second to HBV as the most significant risk factor for HCC, responsible for as many as 20% of global HCC cases. Infection with HCV is often asymptomatic and will typically persist without medical treatment. After decades of infection, unresolved inflammation can agitate the hepatic microenvironment, leading to the development of fibrosis, cirrhosis, and eventually HCC.[69]

The regenerative capacity of the liver allows for the replacement of significant hepatocyte loss caused by injury; however, when liver cells are continually being regenerated, proliferation

can result in the development of inflammation and eventual carcinogenesis. Chemokines and their receptors eliminate viral pathogens but also promote immune-mediated liver inflammation. Within the infected liver, chemokines are secreted to attract a specific and vigorous T cell response to clear HCV; however, in a majority of patients, infection is not resolved. In addition, as was seen for HBV, a non-specific T cell population with a weak and unfocused response unable to eliminate the virus is chemoattracted to the site of infection, resulting in chronic inflammation largely responsible for the long-term hepatic damage associated with chronic hepatitis C.[70]

The LTα and LTβ cytokines and their receptors were shown to be substantially upregulated in HBV- and HCV-induced hepatitis and HCC. Inhibition of the LT signaling pathway in a transgenic mouse model suppressed the formation of HCC.[71] Hepatic LTα and LTβ expression stimulates chemokine production by hepatocytes thereby attracting circulating inflammatory cells that create a toxic hepatic environment of hyperproliferation.[71] In mice, LTα and LTβ expression mimics the stages of fibrosis and inflammation that precede human liver cancer causally linking hepatic LT overexpression to hepatitis and HCC. Blocking this signaling cascade through LTβR-Ig treatment has been shown to partially reverse inflammation, preventing HCC formation in mice with chronic hepatitis and may be effective in human liver pathologies demonstrating sustained LT signaling.[71]

Elevated levels of TNFα and VEGF have also been associated with severity of inflammatory liver disease and were seen in diseased specimens but not in normal specimens. Additionally, serum TNFα levels were significantly higher in all the patient groups than in the healthy volunteers with increasing expression correlating with disease progression. TNFα may therefore serve as a biomarker, and measuring serum TNFα levels may help monitor the progression of liver disease in patients living with chronic hepatitis infection.[72]

Generation of reactive species during inflammatory processes also likely contributes to the pathogenesis of hepatic disease. For example, like 8-OHdG, 8-nitroguanine, which is only formed during periods of inflammation, accumulates in the livers of patients with chronic hepatitis, and increases with severity of inflammation. Therefore, OS markers can potentially serve as biomarkers of inflammation-mediated carcinogenesis related to chronic hepatitis.[73] In addition, expression of both iNOS and COX-2 has been shown to modulate angiogenesis and enhance tumor growth in several tumor types. To evaluate this in HCC patients, immunohistochemical staining was performed using antibodies for iNOS and COX-2, where iNOS was expressed at significantly higher levels in HCV-positive HCCs and COX-2 expression was correlated with iNOS expression and tumor microvessel density, suggesting that both iNOS and COX-2 might be important factors in the pathogenesis of HCV-positive HCCs.[74]

In separate studies, both the HBV protein HBx and HCV core protein have been shown to activate the NF-κB signaling pathway.[75–77] Constitutive activation of NF-κB in the liver is a key event in neoplastic progression. In the MDR2 knockout mouse model, loss of NF-κB regulators led to spontaneous liver injury, fibrosis, and HCC. Interestingly, chronic injury seemed to be sufficient enough to initiate and promote hepatocarcinogenesis in these mice without the presence of mutations in oncogenes or tumor suppressor genes. This evidence not only emphasizes the key role of NF-κB in the progression of hepatic disease processes, but also provides the mechanistic link between inflammation and HCC. Targeting NF-κB in the liver by inhibiting its actions could prove to be effective in eliminating malignant liver cells in both HBV- and HCV-affected patients.

Patients with viral-induced chronic hepatitis are frequently treated with interferons and ribavirin to eliminate or reduce viral replication, effecting a response in ~50% of individuals.[78] Host immune response may contribute to how patients respond to treatment; for example, patients with higher levels of CXCL10 had decreased response or sustained response compared to those with lower levels;[79] pretreatment serum level of CXCL10 >400 pg/mL has been proposed as an effective predictive marker for anti-HCV therapy.[80] Decreased IL-18 levels after IFN treatment were associated with treatment response while persistent IL-18 levels were associated with treatment failure.[81] Thus, anti-viral medications designed to reduce or eliminate viral replication alter the expression of markers of inflammation, improving response to treatment.

Human papillomavirus. HPV is a small double-stranded DNA virus of the *Papillomaviridae* family encompassing ~120 diverse types of viruses that infect the skin and mucosal epithelia. HPV is primarily transmitted through sexual contact including oral sex and is the most common sexually transmitted virus infecting about 50% of sexually active adults in the United States. The various types of HPVs are separated based on their oncogenic potential into low- and high-risk groups, with about a dozen comprising the latter group, including HPV16 and HPV18, which are the most common HPV types of high risk oncogenic potential.[59] HPV16 and -18 account for about 70% of cancers of the cervix, vagina, and anus and for about 30–40% of cancers of the vulva, penis, and oropharynx. Other cancers causally linked to HPV include non-melanoma skin cancer and cancer of the conjunctiva.[82]

As HPV is able to evade the immune system, triggering a series of pro-tumorigenic inflammatory responses, it is likely that chronic inflammation plays a significant role in the development of HPV-associated malignancies. A link between HPV16 infection in patients with head and neck squamous cell carcinoma (HNSCC) and periodontitis, a condition of chronic inflammation where the inflamed periodontal tissue releases inflammatory cytokines into the saliva continuously, has been found, providing evidence that HPV in the presence of inflammatory signals can lead to the development of HNSCC.[83] A smaller study also found an association between

chronic periodontitis and HPV infection in cancers of the tongue.[84] Micro-ulcerations and mucosal damage caused by enduring inflammation may lead to the ideal conditions for initial HPV infection and its persistence leading to proinflammatory cytokine mediated epithelial proliferation and transformation.[85]

Epidemiological studies of sexually transmitted infections provide another link between inflammation and HPV+ cervical cancer. Chlamydia, herpes simplex-2, and bacterial vaginosis are common causes of cervical inflammation and have been associated with an increased risk for cervical tumor formation in the presence of HPV infection.[86–88] Further, an increased secretion of proinflammatory cytokines occurs when cervical cells are co-infected with both chlamydia and HPV and is associated with a more severe environment of inflammation.[89] HPV infection causes the production and circulation of inflammatory cytokines such as IFNs, ILs, TNF-α, and TGF-β. Normally, IFNs have antiviral capability and aid in viral elimination; however, IFNs may stimulate HPV transcription and replication, leading to increased expression of HPV oncoproteins,[90,91] and proliferation of HPV18-positive cervical HeLa cells is stimulated by IFNα2b.[92] In cell culture studies, IL-1, IL-6, and TNF-α expressions have been associated with persistent HPV infection and shown to modulate proliferation of both normal and neoplastic cervical epithelial cells and increase expression of HPV oncogenes,[93–95] while in vivo, elevated levels of IL-6 have been detected in cervical cancer specimens, with IL-6 levels increasing with disease progression.[96] Finally, TGF-β may play a role in HPV-induced carcinogenesis through the promotion of genomic alterations leading to increased instability and oncogenic transformation in HPV-infected cervical cells[97] and by altering the ratio of Tregs and CTLs causing diminished antitumor activity of the CTLs.[98]

Inflammatory cell types have also been implicated in the development of HPV-induced carcinogenesis. For example, TAMs and immature myeloid cells have been shown to impair T lymphocyte activity, resulting in tumor growth promotion in mouse models.[99,100] TAMs expressing MMP9, which is frequently upregulated in cervical cancers, demonstrate proangiogenic actions; suppression of TAM-associated MMP9 expression impaired the formation of new blood vessels and malignant progression.[101] In addition, in HNSCC, tumors from HPV+ patients demonstrated a significant increase in intratumoral infiltration of CD20+ B cells and invasive margin FoxP3+Tregs compared to tumors from HPV–patients.[102]

Epithelial tissues, the primary site of HPV infections, face constant exposure to various sources of OS such as UV radiation, injury, infection, and inflammation. OS and HPV may act synergistically in the development of neoplastic lesions through both anti-apoptotic and pro-survival mechanisms driven by HPV viral proteins, immune cells, and cytokine dysregulation to create an inflammatory environment. For example, inflammation-induced generation of ROS can cause DNA strand breaks, which facilitate the integration of HPV into the host genome.[103] Increased levels of ROS within host cells may be stimulated by the E6* variant protein forms of the HPV viral protein E6, which not only facilitates HPV genomic integration, but also increases the rate of DNA damage.[104]

Human T-lymphotropic virus type 1. Discovered in 1980, HTLV-1 was the first identified human retrovirus, belonging to the family *Retroviridae*. HTLV-1 primarily infects CD4+ T cells, but can also infect other cells of the immune system where it integrates into the host's genome by reverse transcribing its RNA genome into DNA and persists lifelong as a provirus. Transmission of HTLV-I can occur from exposure to contaminated blood, through sexual contact, and from mother to child through breast milk, with routes of transmission varying geographically. HTLV-1 epidemiology data are limited, but it has been estimated to infect 10–20 million people worldwide with endemic regions in Japan, parts of Africa, South America, and the Caribbean.[105]

HTLV-1 infection is associated with several inflammatory diseases and malignancies including spastic paraparesis (HAM/TSP), a chronic inflammatory disease of the central nervous system, a rheumatoid-like arthropathy, and adult T-cell leukemia/lymphoma (ATLL), an aggressive tumor type with poor prognosis. HTLV-1 leads to malignancies and inflammatory diseases by perturbing the host immune system through chronic stimulation of lymphocytes at the cytokine level and dysregulation of their expression. For example, increased levels of IL-13, which acts to regulate immune and inflammatory responses, were found within lymphocytes from HTLV-1-infected patients, and this increased expression was directly related to expression levels of Tax, a viral protein that targets cytokine promoters.[106] Tax has been shown to transactivate the leukocyte-recruitment chemokine macrophage chemoattractant protein 1 (MCP1) through the induction of NF-κB.[107] In a Tax transgenic mouse model, NF-κB-inducible cytokines IL-6, IL-10, IL-15, and IFN-γ were highly expressed, while inhibitors of NF-κB blocked cellular proliferation.[108] High levels of IL-5 and IL-10 are associated with poor prognosis in patients with ATLL, with IL-10 levels increasing with disease progression while IL-5 remained prognostic after multivariate analysis.[109]

HTLV-1 may also induce an inflammatory phenotype through expression of the HTLV-1 bZIP factor (HBZ) gene, found to be constitutively expressed in both HTLV-1 infected cells and adult T-cell leukemia cells. HBZ induces expression of Foxp3, which leads to enhanced proliferation of functionally impaired CD4+Foxp3+ Treg cells, promoting cellular survival and tumorigenesis.[110,111] Further, the development of both T-cell lymphomas and inflammatory diseases in HBZ transgenic mice provides some evidence that HBZ plays a pivotal role in the initiation of these diseases.[112] HBZ also promotes the generation of induced regulatory T cells (iTregs), which convert from Foxp3-expressing cells, which normally

act to suppress excessive immune response, to Foxp3-negative T cells expressing instead the proinflammatory IFN-γ partly mediating the chronic inflammation characteristic of HTLV-1 infection.[113]

Discussion

The six class I carcinogenic viruses described here have very different rates of infection, morbidities, and economic costs worldwide. For example, although ~95% of the world's population has been infected by EBV, in developing countries, infection is usually asymptomatic, while in developed countries, EBV infection leads to mononucleosis.[35] In contrast, infection rates by HBV vary geographically, with significantly higher infection rates in regions such as southeast Asia and sub-Saharan Africa compared to North America, Europe, and Australia (http://www.who.int/csr/disease/hepatitis/whocdscsrlyo20022/en/index1.html), yet infection by HBV is the 10th leading cause of death worldwide, with ~ one million deaths each year attributable to chronic hepatitis, cirrhosis, and HCC.[114] Treatment for HPV-related cancers in the United States alone costs $1 billion dollars annually,[115] thus increased understanding of how these viruses contribute to tumorigenesis and development of new methods to decrease the incidence of viral-related carcinomas are critical.

Preventative measures to decrease viral infection include practicing safe sex, limiting sexual partners, decreased use of intravenous drugs, and screening for viral agents in blood or tissue donations. In addition, vaccines have been developed for both HPV and HBV. A vaccine for HBV was developed in the 1980s, and vaccination of all individuals is recommended to begin in infancy. The HPV vaccine Gardasil®, which protects against HPV types 6, 11, 16, and 18, has been approved for use by the FDA since 2006, and the Centers for Disease Control recommends vaccination of all children aged 11–12 years. Effective vaccines are not yet available for HCV, EBV, HHV8, or HTLV-1. In addition, while antiviral agents have reduced the burden of HCC in HBV- and HCV-infected patients and have shown promising results in treating HPV-related cervical cancers, use of antiviral therapies has not shown significant benefit for refractory EBV-associated lymphoma and post-transplant lymphoproliferative disorder, HHV8-associated KS in AIDS patients, or HTLV-1-associated adult T-cell lymphoma.[116] Given the integral role of chronic inflammation in tumorigenesis, the use of anti-inflammatory agents may prove to be effective in the prevention and treatment of viral-related carcinomas. For example, naturally occurring anti-oxidant and anti-inflammatory compounds such as resveratrol have shown to inhibit carcinogenesis in individuals with HBV and HCV infection,[117] while use of curcumin, found in the spice turmeric, suppressed activation of NF-κB in HTLV-1-infected T-cells.[118] Finally, celecoxib, a non-steroidal anti-inflammatory drug (NSAID) that inhibits COX-2, suppresses invasion and migration of NPC cells.[119] Thus, reduction of chronic inflammation may be an effective method for preventing and/or treating viral-related tumors and decreasing the cancer burden globally.

Author Contributions

Conceived the concepts: JDH. Analyzed the data: ALV, BS, JDH, REE, CDS. Contributed to the writing of the manuscript: ALV, BS, CDS, JDH, REE. Agree with manuscript results and conclusions: ALV, BS, CDS, JDH, REE. Jointly developed the structure and arguments for the paper: JDH, REE. Made critical revisions and approved final version: JDH, REE. All authors reviewed and approved of the final manuscript.

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